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A JOURNAL OF NEUROLOGY

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A Journal of Neurology

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VOLUME LXIII

MACMILLAN AND CO., LIMITED
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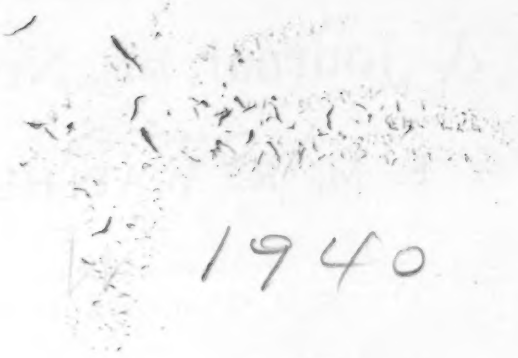

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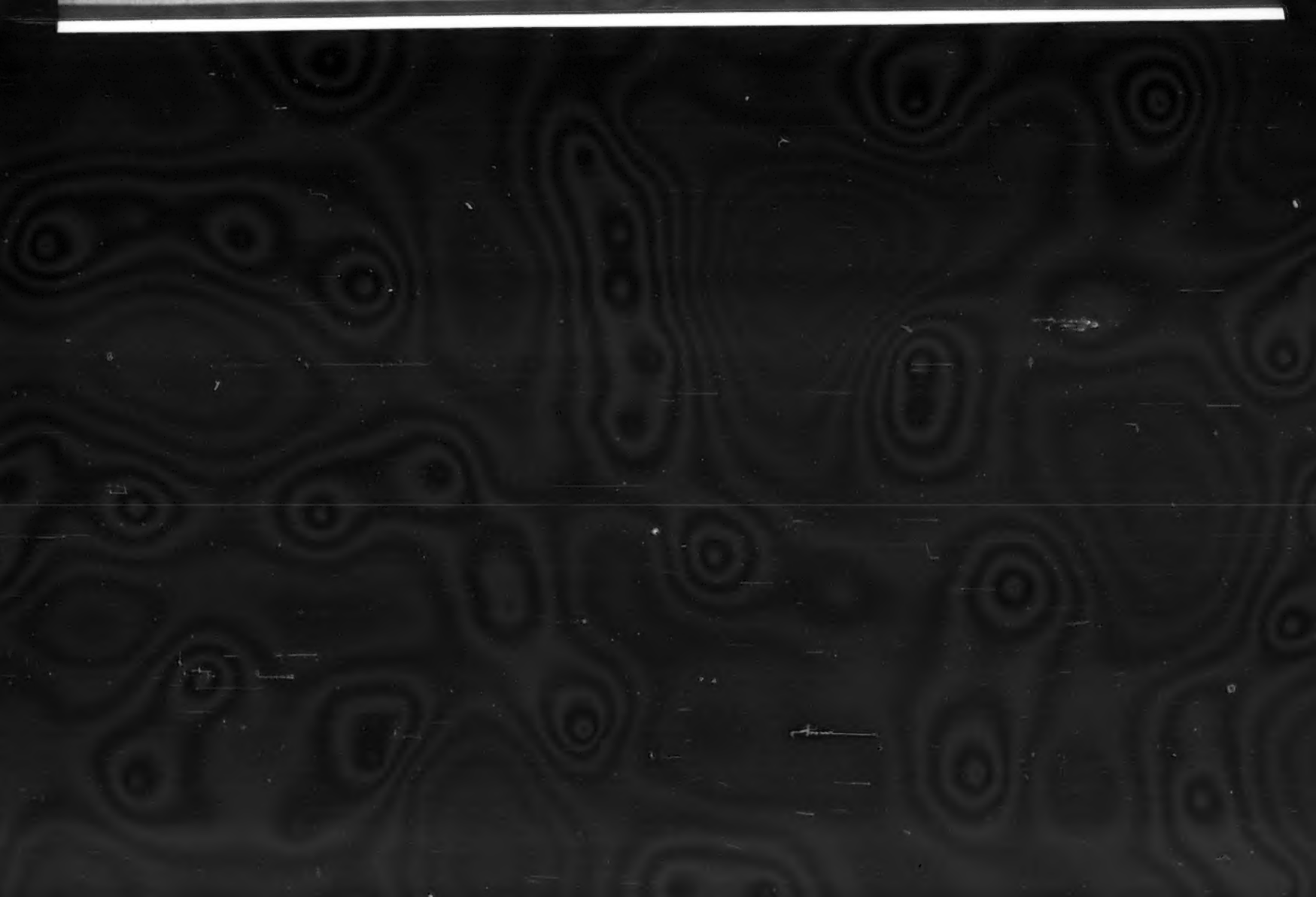

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MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON
NEW YORK: THE MACMILLAN COMPANY

Vol. LXIII. Part 1. 1940 **Price 6s. net. Subscription, 24s. net.**

Entered as Second Class Matter, April 24, 1929, at the Post Office at Boston, Mass., under the Act of March 3, 1897 (Sec. 397, P.L. and R.). Printed in Great Britain.

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All Editorial Communications, Manuscripts and Printed Matter to be addressed to the *Editor*, **F. M. R. WALSHE, M.D., 56, Portland Place, W.1.**

Subscriptions, &c., to be sent to Messrs. MACMILLAN & CO., LTD., St. Martin's Street, W.C.2.

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MARCH, 1940

BRAIN.

PART 1, VOL. 63.

THE FORMS OF GROWTH IN GLIOMAS AND THEIR PRACTICAL SIGNIFICANCE.

BY H. J. SCHERER

(From the Laboratory of Pathology of the Bunge Institute, Antwerp, Belgium.)

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I.—INTRODUCTION.

THE great practical significance of an exact knowledge of the forms of growth and extension of gliomas needs no special emphasis. For both the neurologist and the neurosurgeon this knowledge is certainly one of the most important aspects of the pathology of the gliomas. It is therefore surprising that this aspect of the problem has been rather neglected in modern research on this subject. In fact, the most penetrating observations made in this field are still those found in older papers (f.i. Stroebe, 1895), while most investigators of the last twenty years have been fascinated

by cytological and histogenetic problems to such a degree that they pay little attention to most of the other aspects of the morphology of gliomas. This curious state of things may be accounted for by the fact that modern research on the gliomas has been carried out primarily by neurosurgeons and is very frequently based on the study of small fragments of tissue removed at operations or examined by methods such as supravital coloration, wet film technique, small paraffin sections and silver-impregnated frozen sections, which do not allow the use of large sections throughout the entire tumour. The importance of this factor is illustrated by the fact that the few modern papers which pay some attention to the mode of growth of gliomas have been carried out by pathologists on necropsy material (f.i. Carmichael, 1928).

On the whole, we find scattered throughout the literature many isolated and often contradictory statements regarding the mode of growth and extension of certain kinds, or of isolated cases, of glioma. There are some useful studies of isolated aspects of the problem especially the question of metastasis (Russell and Cairns, 1930 ; Cairns and Russell, 1931 ; Bodechtel and Schüler, 1937 ; Hasenjäger, 1938 ; and others), but so far there has not been one systematic and general study of this important question.

This paper contains the results of the writer's systematic personal researches in this field ; at the same time, the opinions of other authors are referred to when it seems possible to do so without fruitless criticism. The purpose of this paper is not the discussion of pathogenetic questions, but a clear description which may be useful to both clinicians and pathologists. The form of description has been adapted to empirical and not to theoretical considerations. Special care has been given to the study of how much the macroscopically visible limits of the growth of a glioma coincide with its real limits, such as are demonstrated by careful microscopical study. The results of this investigation are not submitted as either complete or definitive, for many details require further special studies.

II.—Definition.

Gliomas being true neoplasms, there is no reason to apply other rules or another terminology in the study of their growth than those used in cancer study in general. The most important question for the clinician, and especially for the neurosurgeon, is to know whether a given tumour has a purely expansive or an infiltrative mode of growth. In the former case the surrounding tissue is only pushed aside by the tumour but never

invaded, with the result that successful extirpation may be practicable, while in the latter all the conditions for recurrence are present. Infiltrative growth is the first and essential condition for malignancy of a neoplasm, while purely expansive growth is the outstanding characteristic of benign tumours. This is, of course, true for gliomas to the same degree as for all other tumours.[1] Thus, the first distinction we have to establish is that between infiltrative and purely expansive growth.

Another distinction plays an even more important rôle in gliomas than in the case of most other neoplasms, namely the distinction between infiltrative and destructive growth. Both are more or less associated in most tumours; but with surprising frequency in gliomas we meet extensive infiltrative growth without any, or with very incomplete, destruction of the pre-existing nervous parenchyma which remains intact in the midst of the tumour tissue. The great influence of this behaviour on the clinical symptomatology of such tumours is evident.

However, it is obvious that this theoretical distinction between expansive, infiltrative and destructive growth does not exhaust all that can be said about glioma growth. Among the most important points for practical purposes, for instance, are the form and the degree of the infiltrative tendency in given gliomas. The invasion may be either very intense and limited to a very narrow zone, or it may consist of a spread of more or less isolated cell elements over a very large area of tissue at a long distance from the compact tumour. In the former case the macroscopically visible sharp limit of the tumour is very likely to coincide with the actual extreme limit of tumour cell spread and a radical operation becomes possible; in the latter case the growth always exceeds the macroscopical tumour limit to such a degree that any attempt at total extirpation must necessarily fail.

There is, finally, a last form of tumour growth the importance and frequency of which have become more and more evident in certain fields of cancer study: namely, the primary systematic diffuse or multicentric neoplastic growth of a given tissue such as is observed in lymphosarcomatosis, in many reticulosarcomas, and in myelomas. Our researches show that this type of glioma growth is not uncommon and that its frequency has been much underestimated hitherto.

[1] In fact, in modern literature on the gliomas it has become customary to call benign the slowly growing tumours or those which show recurrence only a long time after operation. This corresponds in no way to the terminology generally applied in cancer study; a great number of operated breast carcinomas show recurrence or metastases only long years after operation, but nobody calls them benign for this reason.

III.—Material and Methods.

Only necropsy material has been used for this study. After the whole brain has been fixed in formalin, it is cut into 15 to 20 mm. thick frontal slices. All slices showing a macroscopical modification are photographed in order to be compared later with the microscopical sections. Then all slices containing the tumour, from its frontal to its occipital end, with a large amount of macroscopically unchanged surrounding tissue, are included in celloidin. One of the results of my researches being the finding that glioma growth is very frequently much more extensive than the macroscopical aspect leads us to suppose, I now study in each case progressively larger apparently normal parts of the brain. One, or sometimes several, very large thin slices are used for frozen sections, stained and impregnated by the different selective stains used in neuropathology. The celloidin blocks are cut quite deeply from both sides in order to obtain a kind of incomplete serial section study of the whole tumour and surrounding tissues. Up to now, 120 cases of cerebral gliomas have been studied in this way.

IV.—Results.

(1) *Purely Expansive Growth in Gliomas.*

The careful study of purely expansive gliomas shows us that this mode of growth occurs exclusively in one kind of glioma, the so-called *ependymoma*. Most of these tumours that we have seen nowhere show

Fig. 1.—Ependymoma of the fourth ventricle. Clear-cut edge, purely expansive growth. Nissl stain. (Case 123/35.)

the slightest infiltrative growth, but grow in the cavity of the 4th ventricle which they dilate more and more. Their limits, both macroscopically and microscopically, are absolutely sharp (fig. 1) and they are easily detached from the surrounding tissue, at least after formalin fixation, without leaving any remainder of neoplastic tissue. When the dilated cavity

of the ventricle becomes too narrow for further tumour extension, the tumour seeks a way to other preformed spaces, such as the lateral recess or posterior cistern where it continues its growth without invading the nervous tissue. This behaviour is shown even by ependymomas which have such definite characters of active growth as fairly abundant mitoses.

As will be shown later, a similar expansive intraventricular mode of growth is adopted also by certain very malignant and otherwise highly infiltrative gliomas as soon as they reach the cavity of the ventricular system. Since we have not yet had the opportunity of studying extraventricular ependymal tumours, it seems questionable whether this behaviour of the ependymomas is really inherent in the nature of their

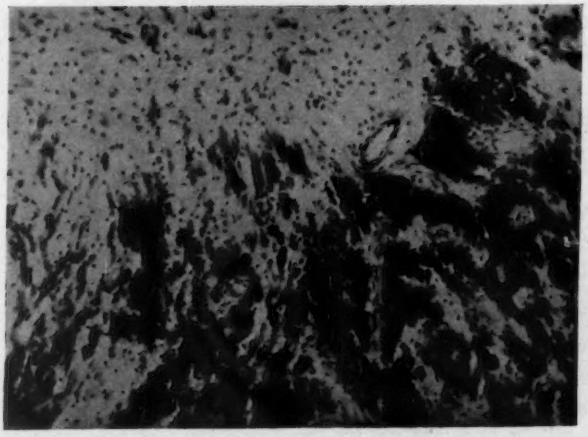


FIG. 2.—Circumscribed infiltrative growth of a fourth ventricle ependymoma with an otherwise purely expansive type of growth. Nissl stain. (Case 52/37.)

growth or is merely an expression of their primary intraventricular localization. However, Fincher and Coon (1929) and later Tönnis and Zülch (1937) emphasize this purely expansive mode of growth in their extraventricular ependymomas of the cerebral hemispheres; thus the local factor of intraventricular growth does not seem to be the essential reason for this behaviour.

On the other hand, we have seen in one otherwise quite typical and expansive ependymoma of the 4th ventricle and lateral recess, the beginning of infiltrating growth at a very circumscribed point near the cerebellar white matter (fig. 2). This proves first that the intraventricular site is not adequate to account for the absence of infiltrative growth in most

ependymomas, and secondly that a minority of ependymomas may become infiltrative, at least at some part of their periphery. In the case cited, this invasion was so limited that for practical purposes it could be neglected. Certain authors (Cairns and Russell, 1931, and others) mention spinal metastases in ependymomas; others (Kernohan and Fletcher-Kernohan, 1937) speak of variations of malignancy so it seems possible that a change in the growth character of ependymomas may in certain instances play an important practical rôle.

The lobulated character of certain ependymomas may involve the compression of surrounding brain tissue between two tumour lobules in the same manner as is observed in meningiomas (Scherer, 1936). It is obvious that this has nothing to do with invasion, though the resulting pictures may give this impression. A careful study of serial sections will always clarify the situation.

On the whole, the mode of growth of most ependymomas being a purely expansive one, this type of tumour satisfies the essential anatomical condition of benignity for a radical operation without recurrence, provided of course, that the situation of the growth in the central nervous system allows a radical intervention.

(2) *Infiltrative Gliomas.*

All the other varieties of gliomas, without exception, have an infiltrative mode of growth, and since ependymomas in the present material form less than 6 per cent. of all gliomas, *infiltrative growth must be regarded as characteristic of the enormous majority of gliomatous tumours.* This, indeed, is the finding in the systematic microscopic study here recorded. However, the kind, degree and extent of this infiltration, its combination with an expansive mode of growth, various secondary influences, &c. give rise to many different appearances. A merely macroscopic or an incomplete microscopic examination gives in many instances the fallacious impression of well-defined or expansive tumours.

(*a*) *Apparently expansive gliomas.*—These are here spoken of as apparently expansive gliomas and they include quite a number of essentially different groups the differentiation of which may have considerable practical importance. Some of these types only have been mentioned in the literature, and that briefly, especially by Carmichael (1928). Although combinations of these different types may occur, we may group them for descriptive purposes as follows:—

(i) Certain gliomas have a very narrow zone of growth which on super-

ficial study hides their infiltrative character. A careful microscopic examination reveals that even in these cases the growth exceeds, at least in certain places, the macroscopically recognizable limits of the tumour. Sometimes myelin pictures have to be studied in order to demonstrate the infiltrative mode of growth by the presence of nerve-fibres running from the uninvaded tissue directly into the neoplasm.

In spite of the presence of this infiltrative mode of growth its limitation to a very narrow zone, when encountered over the whole outline of the tumour, obviously creates conditions favourable to a complete removal in so far as the neoplasm scarcely exceeds its macroscopically visible limits.

FIG. 3.—Very narrow, massive growth zone of a microcellular glioblastoma of white matter. Nissl stain. (Case 1195/32.)

This narrow zone of infiltration has been very frequently observed in oligodendrogliomas, in cerebellar astrocytomas (Bucy and Gustafson, 1939) and in many glioblastomas, especially in the frequent microcellular tumour type of rather small size (fig. 3). However, according to Greenfield and Robertson (1933) there are obviously also more invasive forms of oligodendroglioma with a tendency to extensive intraventricular spread, while for the glioblastomas the extreme frequency of mixed cytological types (Scherer, 1938) makes definite statements of frequency impossible.

The fact that essential differences in growth occur in tumours of a uniform cytological-histogenetic group, such as oligodendroglioma, proves again that cytology alone is by no means sufficient to characterize the

morphological and biological behaviour of a neoplasm. It is evident that to both neurologists and neurosurgeons the common type of oligodendroglioma with a narrow zone of growth must give different symptoms from, and better operative chances than, the rare type with widespread infiltrative growth. The same must be true for glioblastomas. We must emphasize the fact that even at the time of death in the absence of any operation, a fairly considerable percentage of so-called "glioblastomas" are rather small, spherical tumours with a very narrow zone of infiltration —in other words with the same behaviour of growth as most oligodendrogliomas (*see* fig. 4). A size of about 5 by 4 by 6 cm. is encountered in about 20 per cent. of glioblastomas.

FIG. 4.—Limitation of a glioblastoma of the white matter by the cortex. Nissl stain. (Case 248/35.)

Another group with a narrow zone of infiltration is formed by many *medulloblastomas;* this fact has been recorded by Bailey and Cushing (1925) in the following terms: "The lesions have appeared macroscopically . . . to be fairly well circumscribed, though histological study invariably has shown invasion of the surrounding cerebellar tissue." In 1926, these authors write: "The growth, after all, in its early stages . . . does not actively invade the cerebellar tissue," while Wohlwill (1930) emphasizes the essentially infiltrative growth of medulloblastomas. In our experience, medulloblastomas grow predominantly by simple expansion of the cavity of the 4th ventricle, but *always* show at the same time a rather narrow zone of infiltration not only towards the vermis, but also against the floor

of the ventricle. There seem to be differences in the growth of different medulloblastomas which may perhaps coincide with the obvious differences in the clinical behaviour emphasized recently by Cox (1934) and by Craig and Kernohan (1938). In a medulloblastoma of slow clinical evolution (without operation) we found no metastases and only a moderate invasion of the periventricular tissue in spite of the long duration (three years) of the growth.

A last group of tumours with a narrow zone of growth are the so-called "polar spongioblastomas," which, according to Russell and Bland (1934) are identical with Penfield's "piloid astrocytomas." We can confirm this

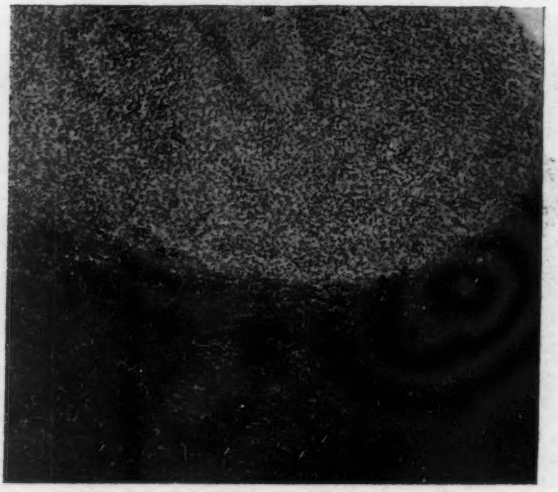


FIG. 5.—Definite arrest of a glioma of the white matter by the cortex. Nissl stain. (Case 222/34.)

identity. In the writer's experience, the narrow zone of growth of these tumours is an essential biological character which obliges us to separate them definitely from the other astrocytomas the growth of which is always diffuse in spite of an identical "histogenesis."

(ii) The growth of many gliomas in large measure respects certain pre-existing structures of the nervous system. The most beautiful and most frequently seen example is the arrest of many gliomas of white matter at the grey substance, especially of the cortex, the striatum, &c.; a phenomenon studied in detail in a former paper (Scherer, 1936). In these instances the form of the tumour is determined by that of the cortex and the limit between the glioma and the cortex is clear cut (figs. 4, 5). In such

cases an incomplete examination of the tumour, limited to its subcortical parts, must give the false appearance of a fairly circumscribed growth, while a complete study often reveals in other places widespread infiltration without any macroscopically visible limits.

In so far as this unexplained influence of both grey and white matter upon the extension of the glioma has as its consequence a fairly clear-cut edge to the tumour, it must, of course, be considered as surgically favourable. Unfortunately it frequently also gives the tumour a very complex outline as the glioma adopts the contour of the grey matter which stops its extension (temporarily at least), and its round shape is transformed into a quite irregular one varying according to its situation. In the subcortical region the result is a digitiform growth of the tumour which sends

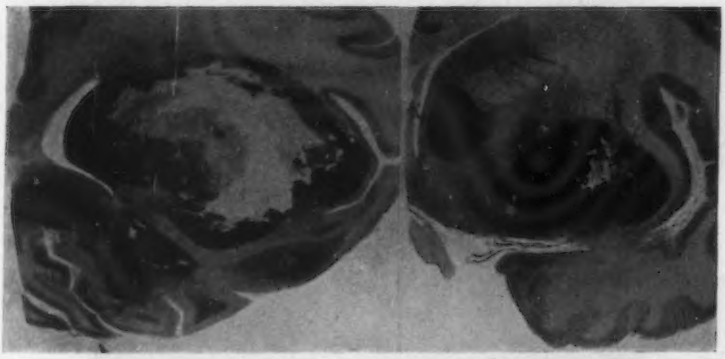


FIG. 6.—A large frontal glioblastoma (at left), growing in the occipital direction, is divided into two prolongations (at right) which respect the grey nuclei of basal ganglia. Nissl stain. (Case 64/37.)

its prolongations into the white axis of some of the convolutions (fig. 14). In the region of the basal ganglia this type of growth may lead to very elongated ramifications. Thus, fig. 6 illustrates a real division of a big frontal orbital glioblastoma into two apparently different tumours owing to the fact that the posterior part of the growth respects the caudate nucleus and the strio-pallidum, growing in a predominantly expansive manner into the internal capsule at one side, and external to the lateral and inferior edge of the putamen on the other. Obviously both clinical symptomatology and surgical treatment are influenced by this behaviour. It is particularly frequent in the group of so-called "glioblastomas" but never occurs in cerebral astrocytomas, the invariably diffuse growth of which does not respect any structure. In cases of growth in the grey

matter respecting the white substance (*see* Scherer, 1936) the result is in principle the same; the practical importance of this last form is very limited owing to its relative rareness.

(iii) The macroscopic appearance of a definite edge is sometimes accentuated by degenerative processes in the borderline of the tumour, producing a split in the zone of growth, and in consequence a certain degree of enucleability. According to Carmichael (1928) whose statements are entirely confirmed by our observations, this enucleation is never complete, because we always find on microscopic examination living glioma tissue outside the split which must lead to recurrence (fig. 7). Carmichael seems

FIG. 7.—Split formation at the tumour edge by degenerative changes on the borderline. There is already a slight tumour cell infiltration outside the split. Van Gieson stain. (Case 1195/32.)

to consider this behaviour as the predominant reason for the circumscribed aspect of so many glioblastomas. In our material this form was rare and plays a much less important rôle in the apparently expansive mode of growth than the factors mentioned under headings (i) and (ii).

(iv) Still rarer is another consequence of gliomatous degeneration, resulting in a real enucleability of the whole tumour with a small capsule of surrounding normal brain tissue. We have observed this phenomenon in two glioblastomas with an enormous central necrosis surrounded by only a small edge of living tumour tissue. The necrosis was encapsulated by a large zone of mesenchymal scar tissue, the numerous vascular trunks of

which were anchored in the surrounding uninvaded brain tissue (fig. 8). In such a case, the whole tumour with normal brain tissue is easily

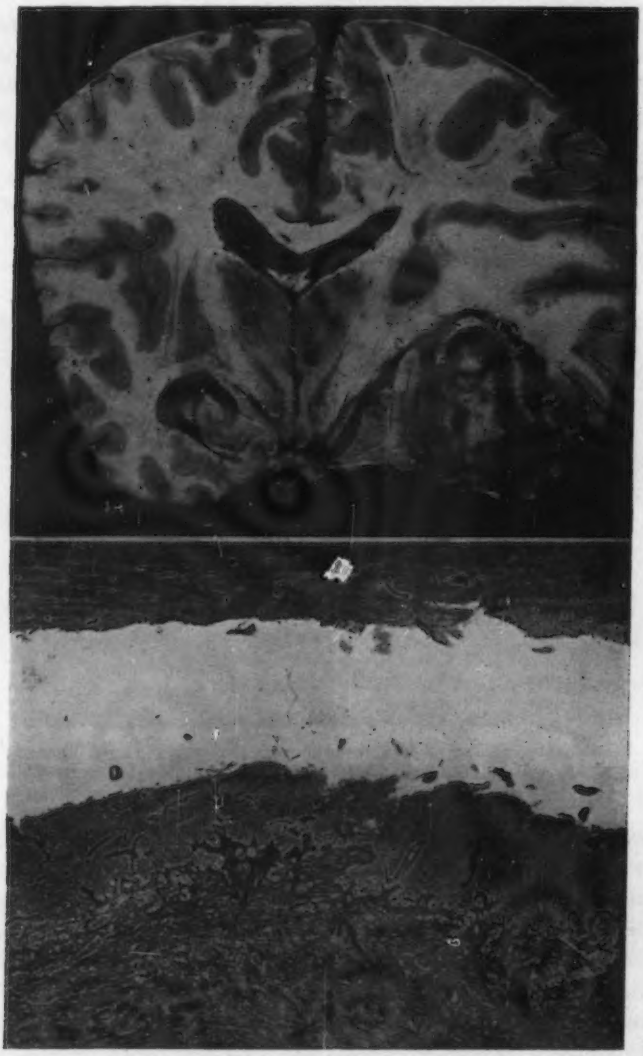


FIG. 8.—Temporal glioblastoma perfectly circumscribed by mesenchymal encapsulation of the large central necrosis. Above: macroscopic aspect; below: Achucarro-Klarfeld stain for mesenchymal fibres, showing below the mesenchymal capsule with a zone of normal brain tissue, surrounded by a split. (Case 247/36.)

enucleated, at least in the formalin fixed brain. In the case illustrated in fig. 8 this enucleability was spontaneous to such a degree that except for the extensive necrosis, the tumour resembled macroscopically a meningioma. The microscopic examination showed a highly polymorphous glioblastoma. Since in this case no tumour tissue remained in the brain after enucleation, the anatomical conditions for a really radical operation seem to have been present. The extreme infrequency with which this behaviour is encountered limits its practical importance. We have observed it in only two instances. It seems worth mentioning, however, since this attempt at auto-cicatrization is a curious kind of spontaneous cure of some theoretical interest. Its rarity is accounted for by the fact that the mesenchymal encapsulation of the common extensive central necrosis in glioblastomas is very rare.

(v) A last important factor which induces a predominantly expansive mode of growth and thus a certain limitation of otherwise infiltrative gliomas is the ventricular system. The *circumscribed intraventricular growth* will be discussed later in a special chapter dealing with the different ways in which the ventricle may influence the growth of a glioma.

(*b*) *Diffuse infiltrative growth in gliomas.*—This chapter does not deal with primary diffuse gliomas but with well-defined compact tumours, the zone of growth of which is very widespread. In contrast to the cases considered under (A), in this group the microscopic examination generally reveals a much more extensive growth than the macroscopic aspect suggests; in other words the macroscopical aspect always misleads us by failing to reveal the real extent of the tumour.

This behaviour is found in a large number of so-called glioblastomas (over half of the present material). Kino (1935) who, for merely histological purposes and without comparative study of the macroscopic aspects, first differentiated the widespread from the massive type of zone of growth, considered a widespread growth as typical of the "magnonuclear" variety of these tumours, while the narrow zone of growth was typical of the giganto-cellular type. Our material does not confirm this ruling. Definite percentages cannot be given because one and the same tumour may show at one place a widespread infiltrative zone, while in other places a narrow zone of growth exists. Further there is no sharp limit between these two extremes and transitions are not infrequent. The only generalization to be deduced from our material, and one that has exceptions, is that the microcellular glioblastomas have more tendency to grow with a narrow, compact zone than the other varieties.

The histological forms of this widespread growth are quite variable. One of the most important, because the most frequent and the least visible on macroscopic study, is the appearance of secondary gliomatous structures (Scherer, 1936, 1938) at a considerable distance from the compact

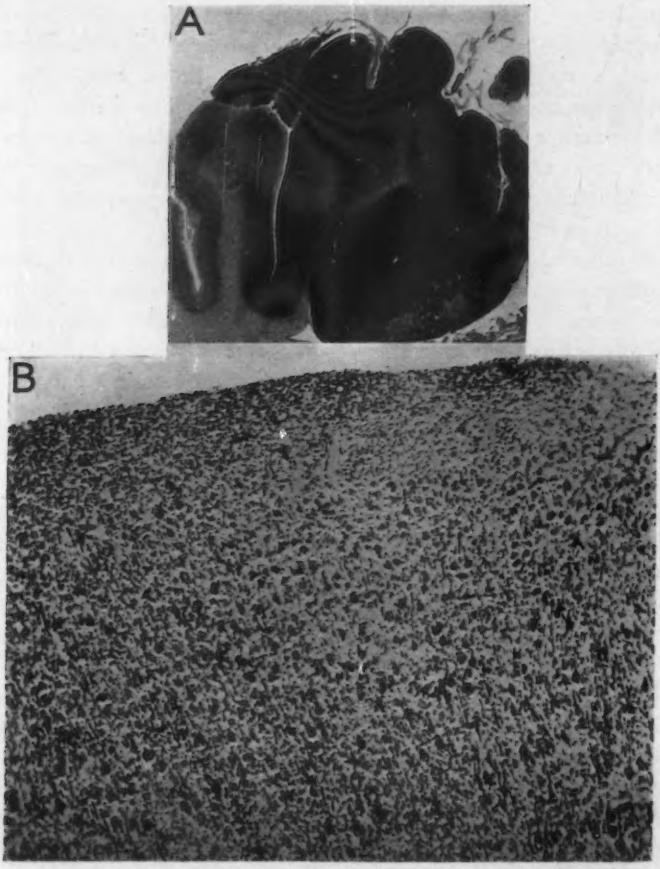


FIG. 9.—(*a* and *b*): (*a*) Small subcortical glioblastoma with diffuse infiltration of the overlying cortex, especially (*b*) by perineuronal secondary structures. Nissl stain. (Case 298/34.)

tumour. These secondary structures are collections of glioma cells concentrated electively about nerve cells (perineuronal growth, Scherer, 1936), vessels (perivascular growth, Scherer, 1937), or nerve fibres

(perifascicular and intrafascicular growth), &c. In their early form these structures appear in an otherwise non-invaded cortex (or striatum, or thalamus) in the neighbourhood of the compact, macroscopically visible glioblastoma of the white matter (fig. 9). They anticipate the massive invasion of these parts by the neoplastic growth. In this type of growth

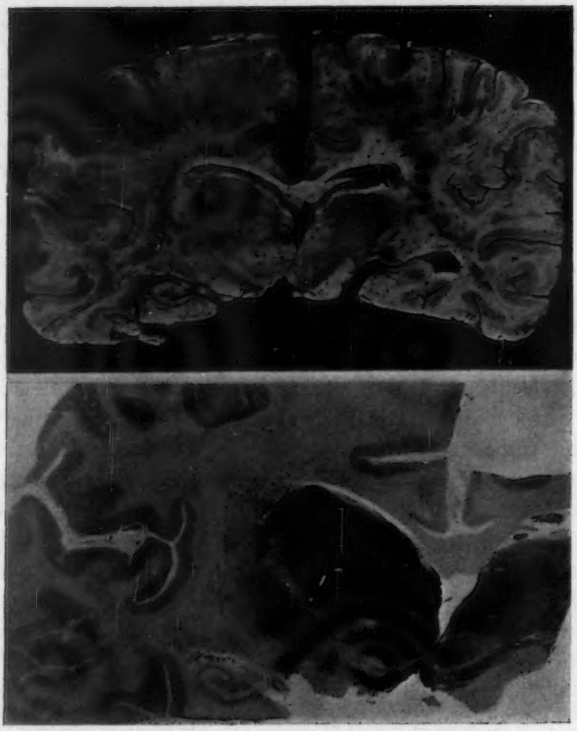


FIG. 10.—Macroscopic aspect (above) and Nissl picture (below) of a thalamic tumour; the macroscopic aspect suggests a unilateral tumour; the Nissl picture shows bilateral growth. Note the multicentric character. (Case 39/38.)

the tendency to spread along the nerve fascicles provokes extensions along the internal capsule into the brain-stem, &c.

A frequent and highly important consequence of this widespread growth is a *bilateral growth of gliomas*. This spreads not only, as frequently emphasized, through the corpus callosum, but also through the anterior commissure and especially in the region of the basal ganglia. Publications dealing with this problem (Alpers and Watts, 1935; Brandes and Cairns,

1936; and others) seem to underestimate the frequency of this phenomenon, probably owing to inadequate microscopic study. In our experience, practically all hypothalamic and thalamic gliomas show microscopically bilateral growth at the time of spontaneous death, although the macroscopic study frequently shows a unilateral tumour only (fig. 10). As in most cases the growth is definitely predominant on one side and involves the other only moderately, a primarily bilateral growth seems unlikely in these instances.

In other cases, especially in certain astrocytomatous tumours with pronounced enlargement of the corpus callosum and involvement of both centra ovalia, we must admit a primarily diffuse bilateral growth; these tumours have thus to be considered in the following section (3) of this Chapter.

If, for practical purposes, we neglect this distinction between primarily and secondarily bilateral gliomas, a distinction which becomes impossible in a certain number of cases, *nearly 30 per cent. of all gliomas show bilateral growth when submitted to complete microscopic study.*

For purely practical reasons we should like to mention also in this chapter the frequent (Scherer, 1938) combinations of true glioblastoma with true astrocytoma of the cerebral hemispheres. A considerable number of these tumours show macroscopically a clearly visible tumour (the glioblastomatous area) surrounded by a zone, often of œdematous aspect, the tumour character of which may seem doubtful, and the limitation of which is never clearly visible (the astrocytoma area). As these tumours are, in our experience, true diffuse astrocytomas which undergo a secondary degeneration of circumscribed parts into glioblastoma, this is just the opposite to the secondary widespread growth of a primary circumscribed tumour dealt with in this chapter.

(*c*) *Extracerebral infiltrative growth in gliomas.*—Gliomatous growth in the meningeal tissue is very frequent, but its extension varies greatly in different types of glioma. The tendency to widespread growth in the meninges is one of the striking characteristics of medulloblastomas (*see* Bailey and Cushing, 1925). In our experience, invasion of the leptomeninges is not less frequent in glioblastomas, but with the important difference that here this invasion remains generally limited to the area where the tumour is in touch with the pia. Such a widespread intrameningeal growth as observed in medulloblastomas is rare in glioblastomas, although it does occur. Astrocytomas also sometimes show true intrameningeal growth. We have observed this behaviour even in a cere-

bellar astrocytoma. Nevertheless, many cerebral astrocytomas do not invade the meninges in spite of the fact that the neoplasm is extensively in direct contact with them. The reasons for this difference of behaviour is still obscure. The spinal meningeal metastases, frequent especially in medulloblastomas but also observed in other gliomas, are a consequence of this intrameningeal growth. As this question has been exhaustively studied by Russell and Cairns (1930) and by Cairns and Russell (1931) the reader is referred to the papers of these authors.

Growth of glioma in the choroid plexus is frequently observed in tumours which invade the ventricle.

We omit any discussion of glioma growth in muscular and subcutaneous tissue of the skull following decompression, &c. because this paper deals only with the spontaneous behaviour of gliomas in the absence of operative influences.

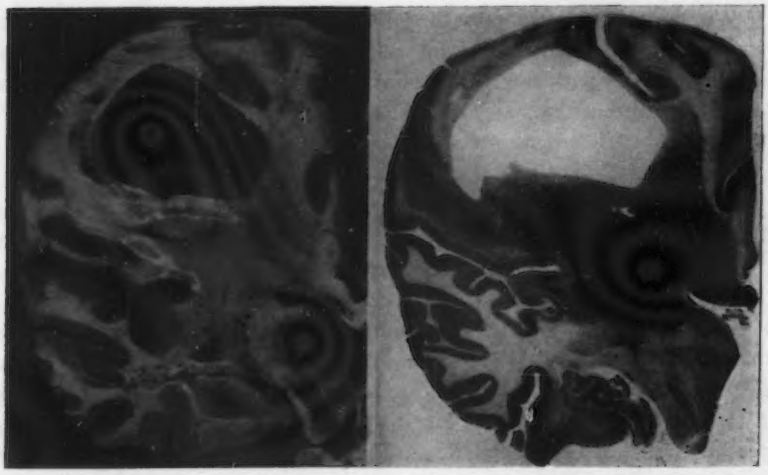
(3) *Gliomas of Primary Diffuse Growth.*

Since the beginning of this century, and up till recently, a certain number of cases of primary diffuse glioma were published under quite different names ("Gliomatous degeneration of parts of the brain," Rindfleisch; "neoplastic form of diffuse sclerosis," Neubürger, 1921; Cassirer and Lewy, 1923; Matzdorff, 1924; "diffuse glioma," Landau, 1910; "gliomatous hypertrophy," Hildebrandt, 1906; "central diffuse Schwannosis," Foerster and Gagel, 1934; v. Santha, 1936; "gliomatosis cerebri," Angyán, 1912; Bielschowsky, 1915; Nevin, 1938; "diffuse blastomatous glial proliferation," Schwartz and Klauer, 1927, &c.). Their common characteristic is a quite diffuse neoplastic growth throughout large parts of the central nervous system without a macroscopically visible circumscribed tumour, and with but insignificant destruction of the pre-existing nervous parenchyma. The fact that most of these cases are published in a purely descriptive manner indicates that the authors consider them as rare exceptions.

The systematic study of gliomatous brains here recorded proves that this is an error. *Primarily diffuse glioma without formation of a definite "tumour" and without pronounced destruction of the pre-existing tissue is encountered in about 25 per cent.*[1] *of gliomas in general. All astrocytomas of the cerebral hemispheres, a considerable number of astro-*

[1] An exact percentage cannot be given because in some instances it is impossible to be sure whether we are dealing with a primarily diffuse process or a secondary diffuse growth of a primarily circumscribed tumour. This theoretically important distinction is, of course, meaningless for practical purposes.

cytomas of the brain-stem, certain rare glioblastomas and a number of tumours which permit of no cytological-histogenetic definition may be included in this type of growth. There are, of course, all degrees of transition from gliomatosis affecting the whole brain and not showing the slightest macroscopic tumour to formations readily recognizable from their macroscop aspect as neoplasms. However, their great extension, their lack of lin ıtion, and their entirely diffuse character without any circumscribed " tumour " caused by local increase of cellularity obliges us to put them in the same group, both for practical as well as for theoretical



(*a*) (*b*)

FIG. 11.—Macroscopic aspect (left) and Nissl picture (right) of a cystic, diffusely growing, parieto-occipital astrocytoma. Macroscopically no definite tumour is visible in the deeper parts of the brain ; microscopically, there is tumour growth through the whole centrum ovale, corpus callosum, capsula interna, caudate nucleus and upper parts of putamen. (Case 466/36.)

reasons. These brain tumours show the same behaviour as lymphosarcomatosis in which we observe all transitions from really generalized cases to more and more " regional " instances affecting only the lymph nodes either of the abdominal or of the thoracic region.

The frequency of these diffuse gliomas has been so greatly underestimated because of the doubtlessly incomplete microscopic examination of most gliomatous brains, complete examination being impossible in operated cases, or neglected in necropsy material the study of which has been limited to macroscopically changed areas. This is more important

for astrocytomas than for other gliomas because the former are often difficult to see or to distinguish from simple œdema (*see* Carmichael). If an astrocytoma be easily recognizable this is generally due to the degenerative changes so commonly encountered, especially microcystic degeneration. The importance of this technical factor is shown by some illustrations. Figs. 11*a* and 11*b* are taken from a typical case of cystic astrocytoma of a cerebral hemisphere. Macroscopically, there is no "tumour," but only a large cyst in the inferior wall of which one sees what is commonly described as a "mural nodule." In the depth of the centrum ovale is to be seen an ill-defined, œdema-like, yellowish discoloration. According to a stereotyped sentence repeated throughout the literature of the gliomas, cystic astrocytomas are perfectly operable provided the mural nodule is extirpated. The neurosurgeon applying this thesis in this case, and receiving histological confirmation of the astrocytomatous nature of the tumour, would be justified in believing in a completely successful extirpation.

The microscopic study of the corresponding brain slice shows that in reality the neoplasm is growing throughout the whole centrum ovale, the corpus callosum, the upper parts of the internal capsule, the putamen and the caudate nucleus!

The microscopic examination proves that in this case, which is one of the smallest cerebral astrocytomas in the present series, complete extirpation is not possible ; *and this is true for all our cerebral astrocytomas without exception.*[1] We must emphasize that we have not seen a single circumscribed cerebral astrocytoma among 120 gliomas. The literature contains a number of short general statements that there exist circumscribed as well as diffuse cerebral astrocytomas (Roussy and Oberling, 1931 ; Bailey and Ectors, 1938 ; Eisenhardt, 1937 ; Courville, 1937 ; Zülch, 1939) ; but not one case is described in sufficient detail for a final judgment to be passed. All authors who have carefully examined necropsy material emphasize the unlimited and diffuse character of the cerebral astrocytomas (Stroebe, Carmichael, Waggoner and Loewenberg). *In these circumstances, the existence of really circumscribed cerebral astrocytomas yet awaits proof by careful description of a completely examined case.* If such cases

[1] We have to make one reservation, namely for the purely "piloid astrocytomas," identical with the "polar spongioblastomas." As pointed out previously these tumours have a rather narrow growth zone. I have not seen such a tumour in the cerebral hemispheres, but Alpers and Rowe (1937), as well as Elvidge, Penfield and Cone (1937) describe piloid astrocytomas in the cerebral hemispheres. If encountered, they certainly have to be separated for biological reasons from the "diffuse" cerebral astrocytomas.

exist, they are certainly exceptional. As a rule cerebral astrocytomas do not allow of a radical, complete extirpation; if their recurrence causes clinical symptoms only after a long interval of years, this is because of the slow growth of the residual parts.

All the cerebral astrocytomas of the present series invaded more than one lobe, a large number were bilateral via the corpus callosum or anterior commissure. Invasion of basal ganglia and of the brain-stem, especially the tegmentum, is not only frequent in astrocytomas of the hemispheres (*see also* Waggoner and Loewenberg), but occurs frequently also in non-astrocytomatous gliomas.

We do not wish to discuss here in detail the more theoretical question as to why this diffuse growth must be considered as a primarily systematic neoplastic process. One of the main reasons for this conclusion was the study of a very diffuse growth of low, uniform cellularity in all its parts, in a case of cerebral astrocytoma, in which the patient died accidentally at the beginning of the clinical course. However, in all such tumours the lack of definite differences in cellularity, decreasing from the tumour centre in the direction of its edge, is difficult to account for on the assumption of the progressive growth of a unicentric tumour.

Apart from cerebral astrocytomas, this primarily diffuse growth is not very common, although more common than the rare recorded examples would lead us to suppose. A special type seems to be formed by a systematized perineuronal, perivascular and surface growth throughout the greater part of the cerebral cortex without definite gliomatosis of the white matter. These cases, although probably separated from typical astrocytomas by their structural and cytological behaviour, have doubtless many points in common with them, especially the clinical symptomatology (e.g. apparently "genuine" epilepsy for long years). Other forms have recently been described by Nevin (1938).

(4) *Multicentric Growth in Gliomas.*

If the primarily diffuse growth belongs essentially but not exclusively to the astrocytomas, multicentric growth is encountered especially, but not exclusively, in the glioblastoma group. But while diffuse growth is one of the essential characteristics of all cerebral astrocytomas, multicentric growth occurs only in a certain percentage (about 20 per cent.) of glioblastomas.

These statements agree with the observations made by Courville (1936) on multicentric gliomas. Courville's paper gives an excellent review of the

whole problem and literature of multiple gliomas, but it limits itself exclusively to the macroscopic aspect of the question. No distinction is made here between macroscopic and microscopic multicentric growth. Both have the same practical importance in that they make a radical operation impossible; for both the theoretical problem, metastasis or primarily multicentric origin, is the same. Although a definite solution of this problem is no easier for multiple gliomas than for multiple myelomas, most observed facts are in favour of primary multiple growth.

A metastatic origin is probable only when we find a large number of very small, rather rounded neoplastic patches disseminated round a large central tumour, and when these patches are not found at a considerable

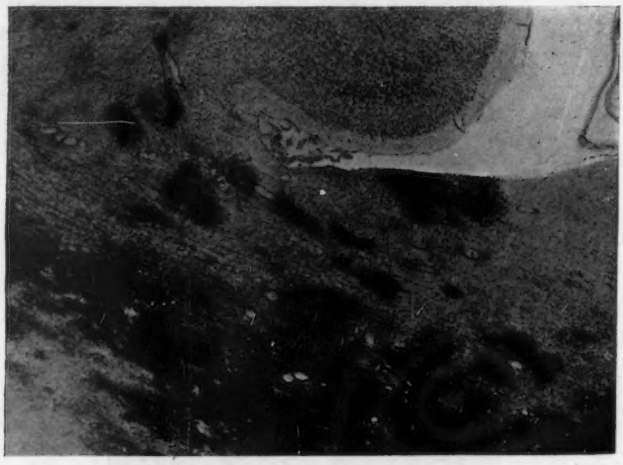


FIG. 12.—Multicentric and probably metastatic growth around a large glioblastoma. Nissl stain. (Case 150/35.)

distance (fig. 12). This behaviour is quite rare and has been observed up to now in three glioblastomas only.

More frequent is another type for which a metastatic origin seems extremely improbable. In these cases, we observe at a considerable distance from a large tumour, one or several large growth zones of glioma whose character of spread (e.g. a rather systematized growth in a part of the cortex) and behaviour toward the pre-existing tissue (growth in the form of secondary structures) is not to be explained by metastasis. Fig. 13 gives an example of this type. In this case we have a fairly circumscribed, large glioblastoma of the occipital lobe. Macroscopically, no other

tumour was visible. Microscopic examination of the brain revealed that this tumour had its frontal end in the centrum ovale at the level of the red

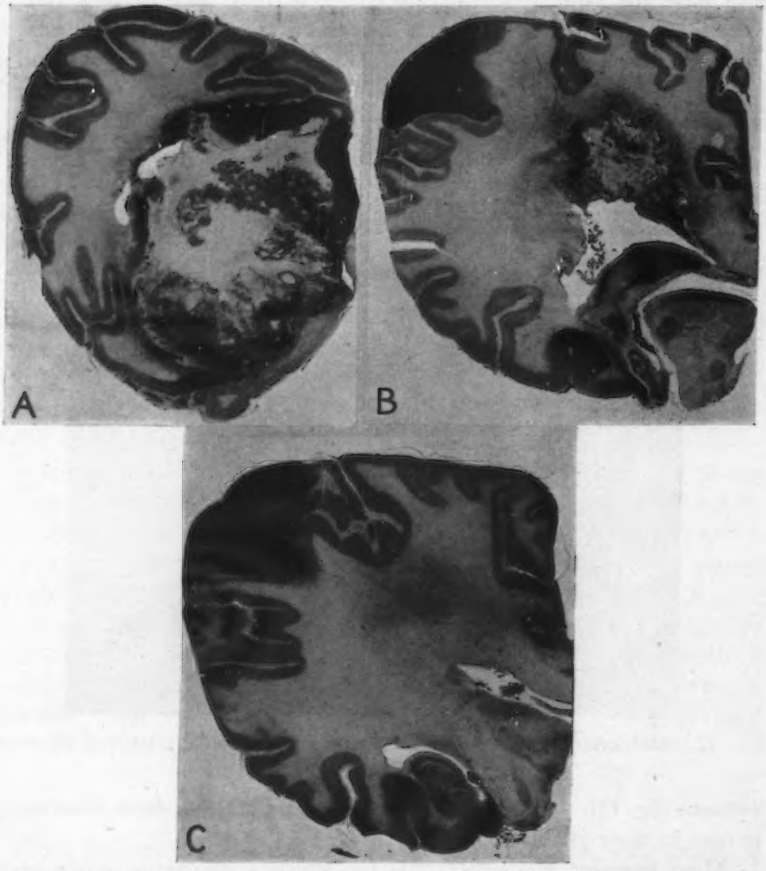


FIG. 13.—A large occipital glioblastoma (*a*), with its frontal end in the depth of the centrum (*b*), surrounded by a large zone of œdema (*c*). Independent of this main tumour the Nissl pictures show macroscopically invisible zones of tumour growth in the parietal and temporal cortex (*b* and *c*) and in the tegmentum (*b*). (Case 340/36.)

nucleus (fig. 13*b*) surrounded by a zone of chronic œdema (fig. 13*c*), but there were four other areas of quite intense, essentially cortical, glioma growth, one of which affected two convolutions at the convexity of the

parietal lobe. Two others were found in the head of the cornu Ammonis and the subicular cortex, and a last zone of slight, but definite gliomatous growth appeared in the tegmentum (fig. 13*b*). The complete study of the case showed that none of these areas had any local contact with the main tumour. All these areas were macroscopically invisible.

In certain cases this multicentricity reaches an extreme degree. Fig. 14 comes from a case of multicentric gliomatosis of a whole occipital and temporal lobe, involving also large adjacent parts of the homolateral parietal lobe and basal ganglia. There was a large main tumour with extensive central necrosis in the occipital lobe, the most frontal parts of

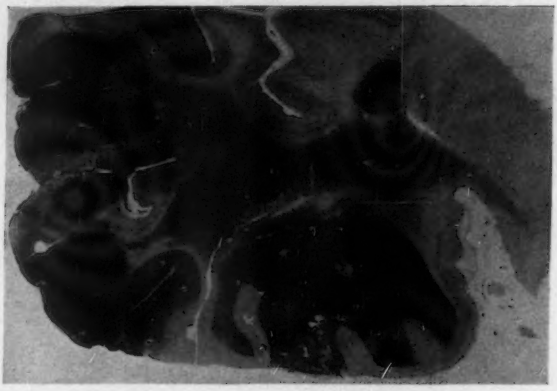


FIG. 14.—Very extensive multicentric grey and white matter growth zones. Note the clear-cut limits of the white matter growth at the basal face of the temporal cortex. Nissl stain. (Case 75/35.)

this are seen in fig. 14 filling the white matter of the basal temporal convolutions, in which the cortex is strictly spared. The other zones of growth show predominantly an elective cortical growth, but patches in the white matter occur also to a considerable extent. In contrast to the former case, the great number and extent of the multiple zones of growth lead to a certain confluence, and most of them are macroscopically visible.

It may be asserted that the *complete* study of a large series of gliomas reveals many more "multiple" gliomas than is generally believed from purely macroscopic study. Multicentric growth in gliomas occurs in at least 10 per cent. of gliomas, though only half of the cases give the macroscopic impression of "multiple gliomas," the other half being a microscopic revelation.

(5) *Influences of the Ventricular System on the Growth of Gliomas.*

One of the conclusions of the present study being the statement that the ventricular system frequently has a considerable though quite variable influence on the growth of gliomas, a special chapter has been devoted to this question. The question is not here discussed in respect of tumours of primarily intraventricular origin, for we have mentioned earlier that in all these cases the result is a purely (ependymoma) or predominantly (medulloblastoma) expansive growth by dilatation of the ventricular cavity, whose walls are or are not invaded according to the general growth tendencies of the neoplasm.

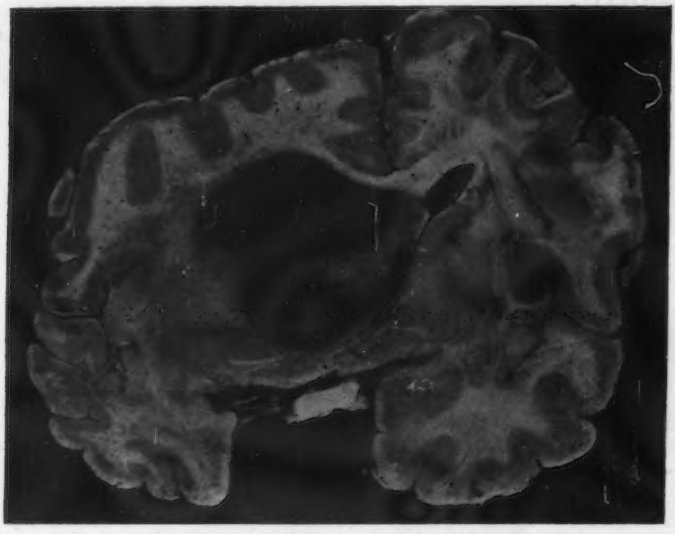


FIG. 15.—Predominantly expansive, circumscribed intraventricular growth of a septum lucidum glioma. (Case 198/38.)

The object of this chapter is the study of the influence of the ventricular cavity on primarily extraventricular gliomas which come into local contact with it. We find four different possibilities:—

(*a*) *The circumscribed intraventricular growth.*—The neighbourhood of the ventricle provokes an intraventricular expansive growth of a glioma, even though the tumour shows a highly infiltrative growth at its place of origin. This form of growth has been specially observed in two situations: tumours originating from the septum lucidum (fig. 15) extend in a predominantly expansive manner in the anterior horn of the ventricle;

tumours originating in the hippocampal region adopt the same spherical shape, by dilatation of the cavity of the temporal horn (fig. 16). We have observed this form of growth in gliomas of quite differing cytology. Fig. 15 comes from a combined oligodendroglioma plus piloid astrocytoma; the tumour of fig. 16 is a microcellular glioblastoma very rich in mitoses. In other words differences of histological "malignancy" cannot account for this tendency of the tumour to circumscribe itself. In every case there was a slight invasion of the ventricular walls in contact with the edge of the tumour, but it was always limited to the immediately subependymal

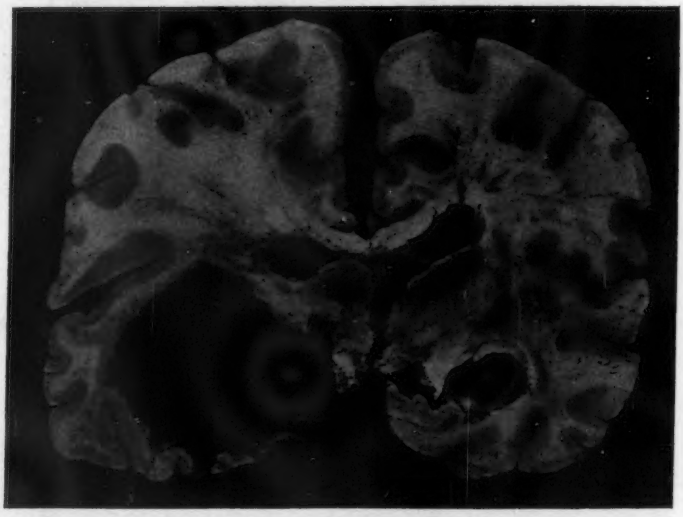


FIG. 16.—Predominantly expansive, circumscribed intraventricular growth of a hippocampal glioblastoma. (Case 284/37.)

region and often developed only in circumscribed areas. This influence of the ventricle is, of course, a surgically favourable one in so far as it limits the expansion of the tumour and gives it a round shape instead of a diffuse irregular form. These cases belong to the group of "apparently expansive gliomas" described in section 2, *a*, of this Chapter.

(*b*) *Diffuse continuous intraventricular growth.*—The opposite effect is rare, viz. that of a glioma reaching a lateral ventricle and growing thence in a diffuse, continuous manner through its whole cavity. We have observed this curious picture in some frontal tumours which invaded the frontal horn and extended thence far in the occipital direction, filling

completely but not dilating, the ventricular space the walls of which were definitely invaded. In one instance (fig. 17), this form of growth reached an extreme degree, the homolateral ventricle was filled up to the tip of the

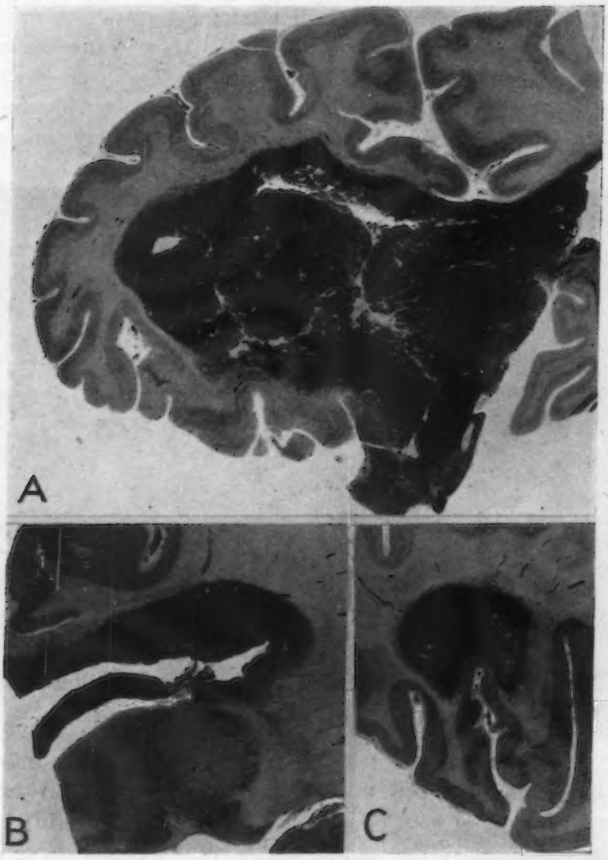


FIG. 17.—Diffuse continuous intraventricular growth of a large frontal glioma (*a*) throughout one whole lateral ventricle (*b*) to its occipital end (*c*). Nissl stain. (Case 299/35.)

occipital horn; the temporal horn, 3rd ventricle and opposite lateral ventricle except its most frontal parts were free, and there were no ventricular metastases at a distance. This type has been found in glioblastomas and in a dedifferentiated astrocytoma; it has been observed by others in

oligodendrogliomas (Martin, 1931 ; Greenfield and Robertson, 1933), and in numerous pineal tumours (cases of Horrax and Bailey, 1925 ; Globus and Silbert, 1931 ; Glaser, 1929 ; De Busscher, 1936 ; Baggenstoss and Love, 1939 ; and others). Obviously this mode of spread is therapeutically quite unfavourable.

(*c*) *Ventricular metastases at a distance.*—This form, first observed in medulloblastomas (Bailey and Cushing, 1925), is the only one which has been adequately studied by different authors (Cairns and Russell, 1931 ; Bodechtel and Schüler, 1937 ; Hasenjäger, 1938), who find that it occurs in quite different types of glioma, e.g. glioblastomas, oligodendrogliomas, astrocytomas, &c. Fig. 18 illustrates extensive ventricular metastases from

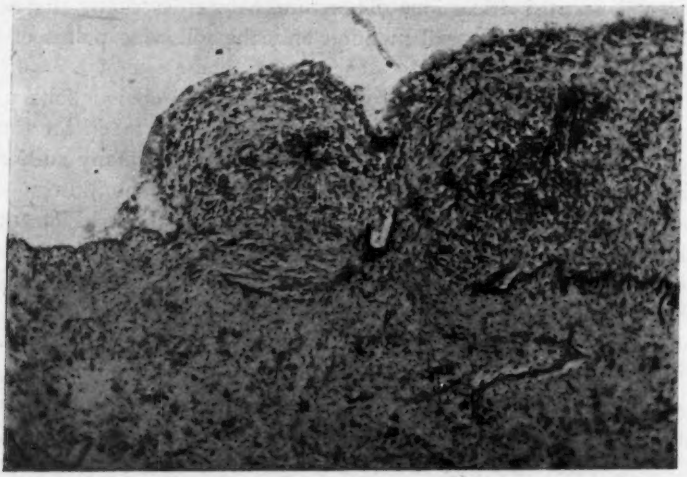


FIG. 18.—Multiple ependymal metastases in a so-called "polar spongioblastoma" = piloid astrocytoma. Nissl stain. (Case 265/38.)

a so-called polar spongioblastoma (piloid astrocytoma) of the thalamic region. In our experience, ventricular metastases at the time of spontaneous death are at least as frequent in glioblastomas as in medulloblastomas provided they reach the ventricular system.

(*d*) Finally, the ventricles may be invaded by gliomas without influencing the latter's growth. In these cases the tumour fills the cavity without dilating it and continues its growth without any change. Thus, we have observed glioblastomas of the hippocampal region filling the temporal horn and surrounding tissues without showing the slightest modification of growth and extension.

The reasons for these contrasting influences which the ventricular system is able to exert on different gliomas still remain obscure. The cytological aspects of these tumours certainly furnish no satisfactory explanation.

(6) *Relations between Infiltrative and Destructive Growth in Gliomas.*

Generally the parenchyma of organs invaded by neoplastic tissue is rapidly destroyed, while the stroma may present either hyperplasia or destruction. In gliomas, the destruction of the pre-existing nervous parenchyma, both nerve cells and nervous fibres, is by no means a general rule. The opinions encountered in the literature upon this question are extremely contradictory; their great number would provide material for endless and detailed discussion. Therefore, before describing the results of our own researches we will mention only the following points of view expressed in the literature.

Until within the past year or so, we encounter the obvious fallacy that pre-existing nerve cells included in gliomas have been taken for tumour elements. This accounts for the surprise expressed by many authors on finding so many " gangliogliomas " in their material. Many illustrations of Globus's (1938) recent paper show what are without doubt inclusions of pre-existing nerve cells in purely gliomatous tumours. It is evident that some authors consider the destruction of pre-existing nervous tissue by invading gliomas as so absolute a rule that they do not even consider any other possibility.

Others believe that the preservation of the nervous parenchyma in the midst of the glioma tissue occurs only in certain well differentiated gliomas, but not in other more "malignant" types. Foerster and Gagel (1939) in a recent paper go so far as to identify a tumour (Case 6) as an astrocytoma in spite of its histological resemblance to a glioblastoma because nerve and glial fibres were preserved in it.

We may sum up our own experiences in the following terms: *In no other variety of tumour is infiltrative growth less frequently associated with destruction of the pre-existing parenchyma than in the case of gliomas of all varieties of histological structure.* Doubtless the preservation of nerve cells and nerve fibres is most frequent, most complete and longest maintained in astrocytomas and the other primarily diffuse neoplasms described in section 3 of this Chapter. In these cases destruction may be practically absent, or very limited, even after long years of clinical evolution and in spite of a relatively rich cellularity of the tumour tissue. But this is not a general rule, for many highly polymorphous glioblastomas

contain perfectly preserved nerve cells and nerve fibres in areas already densely infiltrated. Such behaviour does not, therefore, allow of the diagnosis of astrocytoma.

Why certain glioblastomas show a much more destructive growth than others is not yet known. As Cox (1933) points out, the pre-existing nerve tissue suffers probably much more from degenerative changes occurring in the tumour than from the invasion of tumour cells. That neurofibrils are more resistant than myelin sheaths is a general rule in neuropathology; the recent study of König (1937) as well as our own observations confirm this rule for gliomas of quite different type. On the other hand, for the last forty years numerous authors have emphasized the fact that the pre-existing stroma, especially glial fibres, may not only persist, but even proliferate in the midst of infiltrative gliomas. Thus, the simple presence of glial fibres in a glioma does not help in classification. Recently this question has been studied again by Cox (1933).

V.—General Discussion.

The results of our systematic researches on the modes of growth of gliomas prove the need for a *complete* histological study of every case. The comparison of the macrophotographs of slices of the formalin fixed brain with the photographs of corresponding large histological sections shows that it is in many cases impossible to judge the real extent of a tumour without microscopic examination. This difficulty must be infinitely greater for the neurosurgeon working on the living brain under technical difficulties of observation. The general tendency to underestimate the extent of gliomas certainly reflects the clinical experience of the neurologist, for the relatively slight destruction of the invaded nervous parenchyma which is found in so many gliomas must limit the clinical symptoms of many tumours to those arising from a region much smaller than that actually affected by the glioma. Thus both the clinical and the morphological aspects combine in many cases to prevent the recognition of the real extent of the tumour.

The excessive emphasis on exclusively histological methods which characterizes modern glioma research has unfortunately obscured many ideas which had been clearly established forty years before by authors who knew perfectly well that pure histology is not pathology, but only one of the methods of pathology. This becomes obvious if one compares the admirably clear statements made by Stroebe (1895) and other older authors

on the essential differences in growth between glioblastomas and cerebral astrocytomas [1] with the extremely confused and contradictory opinions expressed by modern authors on this question. In certain respects the present study takes up the problem where Stroebe left it. His material was extremely small, but quite completely studied, although, of course, with quite other methods than those used here. That he was able to draw such valuable conclusions from his small material proves again that a careful objective study of a limited material gives better results than superficial, schematic and inadquate study of large numbers of cases.

The present complete study of a considerable material confirms, firstly, the statement made by Stroebe on the fundamental differences of growth between cerebral astroyctomas and glioblastomas: the former are always primarily diffuse neoplastic processes, showing no "tumour" recognizable as such, unless degenerative changes lend them a tumour-like aspect; of the latter at least the great majority are easily visible, rather well-defined tumours of progressively extensive growth. Glioblastomas which by the period of death reach such enormous dimensions as are shown by practically all cerebral astrocytomas are infrequent. At least 20 per cent. of our glioblastomas were comparatively small tumours (measuring about $4 \times 6 \times 5$ cm.), of spherical shape, and their narrow growth zone provided rather favourable anatomical conditions for radical extirpation. The statement frequently encountered in modern literature, that trespass on the other hemisphere through the corpus callosum is especially characteristic of glioblastomas, is also incorrect; the proportion of cases of this bilateral spread is higher among the astrocytomas than among the glioblastomas.

In grouping our glioma material according to the existence of purely expansive, infiltrative and primarily diffuse or multicentric growth, we obtain the following results:—

With the sole exception of ependymomas, there are no gliomas with purely expansive growth; in other words, *all gliomas except ependymomas show the type of growth which must be considered as the essential anatomical factor in malignancy* (Ewing), because it is this type which makes the successful radical extirpation of a tumour difficult. Modern glioma literature, even works of the highest authority (e.g. Bailey, 1933), frequently emphasize the fact that in a given type of glioma "no capsule is formed," while this is not mentioned for other types. *We must state emphatically*

[1] Stroebe used, of course, other names (glioma for astrocytoma, gliosarcoma for glioblastoma), but his description is absolutely clear and thus allows an immediate identification.

that we never have seen a glioma which formed a capsule, glial or mesenchymal, such as benign tumours in other organs generally form. The rare cicatrization mentioned in Chapter IV (section A.iv), has of course nothing to do with such a primary encapsulation.

On the other hand, our researches show that the infiltrative tendency of many gliomas is limited in a certain degree by numerous factors which we have analysed in the chapter relating to "apparently expansive growth." These factors, by somewhat circumscribing the tumour, play a favourable rôle; on the other hand, by hiding the infiltrative character on macroscopic examination they favour errors concerning the true limits of the tumour. For that reason the knowledge of these factors may have some practical importance. The main factors of this kind are:—

(1) A narrow zone of infiltration encountered in many glioblastomas, in most oligodendrogliomas, in medulloblastomas (before they reach the meninges), in most cerebellar astrocytomas, and in the so-called "polar spongioblastomas" (piloid astrocytoma.)

(2) An arrest of the glioma growth at given pre-existing structures, especially in white matter glioblastomas at the limit of the cortex or deeper grey matter.

(3) Degenerative processes at the edge of the tumour.

(4) A circumscribed and predominantly expansive mode of growth in the ventricular cavity by tumours located in the neighbourhood of the ventricle (hippocampus, septum lucidum, &c.), encountered in glioblastomas, oligodendrogliomas and others.

None of these factors plays a rôle in the cerebral astrocytomas which represent a primarily diffuse type of growth. Multicentric growth, on the other hand, is found in about 20 per cent. of glioblastomas.

On the whole, circumscribed gliomas are certainly rarer than more diffuse forms; the former include nearly 30 per cent. of our entire material, and are predominantly glioblastomas, oligodendrogliomas and cerebellar astrocytomas. About 60 per cent. of all gliomas are rather diffuse tumours invading more than one lobe and showing quite irregular outlines and no definite limits. Nearly 25 per cent. are primarily diffuse processes (all cerebral astrocytomas, other diffuse "gliomatoses," rare glioblastomas). The remaining 35 per cent of tumours show what is probably a secondary diffuse spread (many glioblastomas, some oligodendrogliomas and others). The type of growth found most frequently in this diffuse spread consists of the different "secondary structures." Ten per cent. (nearly exclusively glioblastomas) show multicentric growth. Thirty per cent. of all gliomas are bilateral.

These rough figures indicate another result of our researches: gliomas with a uniform cytological structure frequently show a quite different growth behaviour. As the type of growth is extremely important, not only for pathological classification, but also for clinical symptomatology and especially for neurosurgical prognosis, this is again a striking proof that cytological or histogenetic studies and classifications of the gliomas cannot by themselves characterize the biology of a neoplasm.

As pointed out in the introduction, this study is not a simple description of morphological facts for the use of pathologists, but rather attempts to give some indications which may be helpful to the clinician and especially the neurosurgeon. The pathologist, of course, has a natural tendency to overestimate the importance of morphological factors such as forms of growth for the good or bad prospects of surgical treatment, which in reality depend at least as much upon physiological factors (tendency to bleeding, to post-operative swelling, &c.) which escape the pathologist. It is obvious, however, that the present-day conception of the operative chances of given kinds of gliomas (apart from their location) is based mostly on purely statistical statements and not on a systematic analysis of the reasons of this behaviour; that differences of cellular differentiation are not a sufficient explanation, except perhaps of the rapidity of growth, seems evident. In these circumstances we may reasonably hope that the present analysis of the forms of growth may have some practical use. It explains how cerebral astrocytomas cannot be radically extirpated, for they have a slow but diffuse growth from the beginning, the limits of which are macroscopically invisible. As the possibility of extirpation depends not upon the rapidity of growth, but upon form and visibility, the recurrence of these neoplasms cannot be stopped by surgical intervention. It explains how cerebellar astrocytomas with their narrow zone of growth offer a much better chance for radical operation in spite of their identical cellular aspect and "histogenesis." It shows that considerable numbers of glioblastomas have not only the same narrow zone of growth which favours the complete extirpation of most oligodendrogliomas, but at the same time a moderate size, round shape and macroscopically clearly visible limits. In other words, the anatomical conditions for radical extirpation seem to be present in this type, which forms about 20 per cent. of glioblastomas. Although we realize that physiological factors may partially neutralize these favourable conditions, they form perhaps the anatomical justification of the positive standpoint accepted by Cushing (1937) towards operations on glioblastomas —at least for a proportion of them.

VI.—Summary.

The mode of growth of 120 necropsy cases of glioma was studied by means of large celloidin sections including the whole tumour with surrounding tissues from one end of the glioma to the other (incomplete serial section study). This method is indispensable because the true limits and extent of most gliomas are not macroscopically visible. The great majority of gliomas are more extensive than their macroscopic aspect might lead us to suppose.

Only one rare kind of glioma shows a purely expansive mode of growth, the ependymoma. However, even in rare cases of ependymoma, a circumscribed infiltrative form of growth has been observed.

All the other gliomas, without exception, show an infiltrative type of growth, although in widely differing degrees. This degree by no means corresponds to the more or less "malignant" aspect of the glioma cells. On the contrary, cerebral astrocytomas are the most invasive of all cerebral tumours, while glioblastomas include a considerable percentage of fairly well-defined neoplasms with a narrow zone of growth. The cytological tumour entities include gliomas of quite different types of growth; thus proving yet again that cytology and histogenesis are insufficient to characterize the biological behaviour of a given glioma.

Only about 30 per cent. of all gliomas are relatively circumscribed tumours the real extent of which exceeds but moderately their macroscopically visible limits. This group includes oligodendrogliomas, about 20 per cent. of glioblastomas, many cerebellar astrocytomas and certain medulloblastomas. Factors underlying this surgically rather favourable mode of growth are: (1) a narrow, compact zone of growth; (2) a halting of the tumour at certain pre-existing structures, especially the cortex; (3) degenerative processes at the edge of the glioma. Tumours of the hippocampal region and the septum lucidum grow frequently in the form of round, expansive masses in the ventricular cavity.

About 60 per cent. of all gliomas have a more diffuse character with a widespread zone of growth considerably exceeding the macroscopically visible "tumour," and involving more than one lobe. Nearly 35 per cent. show what is probably a secondary diffuse growth (especially in the form of "secondary structures"), while 25 per cent. must be considered as primarily diffuse neoplastic processes forming no circumscribed tumour. All cerebral astrocytomas, without exception, belong to this group. In the common case of malignant dedifferentiation of an astrocytoma into a glioblastoma, often the glioblastoma alone is visible as a macroscopic

"tumour," surrounded by a large astrocytoma zone the true character of which is discovered by microscopic examination only.

About 10 per cent. of all gliomas—most of them belonging to the glioblastoma group—show a primarily multicentric type of growth ; in half of the cases this multicentricity is only visible on complete microscopic study, the macroscopic examination showing only one main tumour.

Infiltration and destruction by growth are by no means necessarily associated in gliomas. Long-continued preservation of nerve cells and nerve fibres in the midst of tumour tissue is not specific for astrocytomas (although most constant in this group) but occurs also in glioblastomas.

The practical importance of these various findings is discussed.

REFERENCES.

ALPERS, B. J., and WATTS, J. W. (1935), *Arch. Neurol. Psychiat.*, **34**, 1250.
ALPERS, B. J., and ROWE, S. N. (1937), *Amer. J. Cancer*, **30**, 1.
ANGYÁN, J. VON (1912), *Z. Neur.*, **8**, 1.
BAGGENSTOSS, A. H., and LOVE, J. G. (1939), *Arch. Neurol. Psychiat.*, **41**, 1187.
BAILEY, P. (1933), "Intracranial Tumours." London.
BAILEY, P., and CUSHING, H. (1925), *Arch. Neurol. Psychiat.*, **14**, 192.
——(1926), "Tumors of the Glioma Group." Philadelphia.
BAILEY, P., and ECTORS, L. (1938), *Rev. Neurol.*, **70**, 459.
BIELSCHOWSKY, M. (1915), *J. Psychol. Neurol.*, **21**, 353.
BODECHTEL, G., and SCHÜLER, K. (1937), *Dtsche. Z. Nervenheilkunde*, **142**, 85.
BRANDES, W. W., and CAIRNS, A. B. (1936), *Arch. Pathol.*, **21**, 655.
BUCY, P., and GUSTAFSON, W. A. (1939), *Amer. J. Cancer*, **35**, 327.
CAIRNS, H., and RUSSELL, D. S. (1931), *Brain*, **54**, 377.
CARMICHAEL, E. A. (1928), *J. Pathol. and Bact.*, **31**, 493.
CASSIRER, R., and LEWY, F. H. (1923), *Z. Neur.*, **81**, 290.
COURVILLE, C. B. (1936), *Amer. J. Cancer*, **26**, 703.
——(1937), "Pathology of the Central Nervous System." Mountain View, California.
COX, L. (1933), *Amer. J. Pathol.*, **9**, 839.
——(1934), *The Medical J. of Australia*, 182.
CRAIG, W. M., and KERNOHAN, J. W. (1938), *J. Amer. Med. Assoc.*, **111**, 2370.
CUSHING, H. (1937), "Tumeurs intracrâniennes." Paris.
DE BUSSCHER, J. (1936), *J. Belge de Neurol.*, **36**, 375.
EISENHARDT, L. (1937), *Proceed. Assoc. for Research in Nerv. and Mental Disease*, **16**, 390.
ELVIDGE, A., PENFIELD, W., and CONE, W. (1937), *Ibid.*, **16**, 107.
EWING, J. (1928), "Neoplastic Diseases." Philadelphia and London.
FINCHER, E. F., and COON, G. P. (1929), *Arch. Neurol. Psychiat.*, **22**, 19.
FOERSTER, O., and GAGEL, O. (1934), *Z. Neur.*, **151**, 1.
——(1939), *Ibid.*, **166**, 497.
GLASER, M. A. (1929), *Brain*, **52**, 226.
GLOBUS, J. H. (1938), *Amer. J. Cancer*, **32**, 163.
GLOBUS, J. H., and SILBERT, S. (1931), *Arch. Neurol. Psychiat.*, **25**, 937.

GREENFIELD, J. G., and ROBERTSON, E. G. (1933), *Brain*, **56**, 247.
HASENJÄGER, TH. (1938), *Z. Neur.*, **161**, 153.
HILDEBRANDT, K. (1906), *Virchows Archiv*, **185**, 341.
HORRAX, G., and BAILEY, P. (1925), *Arch. Neurol. Psychiat.*, **13**, 423.
KERNOHAN, J. W., and FLETCHER-KERNOHAN, E. M. (1937), *Proceed. Assoc. Research Nervous and Mental Disease*, **16**, 182.
KINO, F. (1935), *Z. Neur.*, **153**, 680.
KÖNIG, A. (1937), "Uber Verhalten der Achsenzylinder und Markscheiden bei Gliomen der weissen Substanz." In. Diss., Hamburg.
LANDAU, M. (1910), *Frankfurter Z. Pathol.*, **5**, 469.
MARTIN, J. P. (1931), *Brain*, **54**, 330.
MATZDORFF, P. (1924), *Z. Neur.* **91**, 489.
NEUBÜRGER, K. (1921), *Ibid.*, **73**, 336.
NEVIN, S. (1938), *Brain*, **61**, 170.
——(1938), *Journal of Neurology*, **1**, 342.
PENFIELD, W. (1931), *Arch. Neur.*, **26**, 745.
——(1932), "Cytology and Cellular Pathology of the Nervous System," **2**, 421.
RINDFLEISCH, quoted after STROEBE.
ROUSSY, G., and OBERLING, CH. (1931), Atlas du Cancer, Fascicules 9 et 10.
RUSSELL, D. S., and BLAND, J. Q. W. (1934), *J. Pathol. and Bact.*, **39**, 375.
——and CAIRNS, H. (1930), *Ibid.*, **33**, 383.
SANTHA, K. VON (1936), *Z. Neur.*, **154**, 763.
SCHERER, H. J. (1936), *Bull. Assoc. Franç. Etude du Cancer*, **25**, 451.
——(1936), *Ibid.*, **25**, 470.
——(1936), *Revue Neurol.*, **66**, 307.
——(1936), IIme. Congrès International Cancer, Bruxelles, Communications, **2**, 250.
——(1937), *Bull. Assoc. Franç. Etude du Cancer*, **26**, 274.
——(1938), *Amer. J. Cancer*, **34**, 333.
——(1938), *J. Belge de Neur.*, **38**, 783.
SCHWARTZ, PH., and KLAUER (1927), *Z. Neur.* **109**, 438.
STROEBE, H. (1895), Zieglers Beiträge, **18**, 405.
TÖNNIS, W., and ZÜLCH, K. J. (1937), *Zbl. Neurochirurgie*, **2**, 141.
WAGGONER, R. W., and LOEWENBERG, K. (1937), *Arch. Neurol. Psychiat.*, **38**, 1208.
WOHLWILL, FR. (1930), *Z. Neur.*, **128**, 587.
ZÜLCH, K. J. (1939), *Fortschritte d. Neurologie*, **11**, 121.

PYRAMIDAL LESION IN THE MONKEY.

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ORIGINAL usage designated as pyramidal the fibres which make up the bulk of the medullary pyramids. When Türck (1851) first employed the term "Pyramidenstrang" he recognized the cortical origin of some at least of the fibres, but as late as 1876 Flechsig justified the use of the term as not prejudicing the origin of the tract. Increasing knowledge has shown that the group of fibres thus designated pyramidal is, in fact, a structural entity. On the one hand it includes all the fibres descending from the cerebral cortex to the spinal cord; and on the other hand, no fibres destined for the cord other than those originating in the cerebral cortex. Thus "pyramidal" has become synonymous with "corticospinal." From time to time other courses for some of the corticospinal fibres have been described both in the cat and in man, though not to my knowledge in the monkey, but these are instances of anatomical anomaly.

The fibres descending from the cerebral cortex to the spinal cord, constituting the corticospinal or pyramidal tract, are nowhere found as a completely segregated bundle, but in the medullary pyramids the admixture of other fibres is minimal. Above this level the corticospinal fibres are associated with other descending cortical systems. Below, descending systems from cortical and from subcortical levels intermingle. Severing the medullary pyramids offers, therefore, a unique opportunity to interrupt corticospinal action, and very nearly that alone; and thus to establish both the symptomatology of pyramidal lesion, and, by reinterpretation, the functions of the pyramidal tract.

Severing the medullary pyramids is an experiment which has been repeatedly attempted with varying success, most recently by myself (1935) on cats. Two previous attempts have been made on the monkey. Rothmann's endeavour (1902; 1907) has no value both because of his approach—from the dorsal surface, splitting the medulla in the mid-line in an effort to sever the decussation of the pyramids—and because of the lack of all

[1] Aided by a grant from the Rockefeller Foundation.

anatomical control, even of gross inspection, of the lesions. Nevertheless his own subsequent cortical stimulations demonstrated the incompleteness of the lesions by the survival of discrete movement of digits. In contrast, Schüller's (1906) work was well conceived surgically, using a ventral approach, and adequately controlled anatomically by Marchi preparations. The lesion in one of his two monkeys was considerably more than complete ; in the other, considerably less. Unfortunately Schüller was more concerned with exposing Rothmann's errors than in examining the effects of pyramidal lesion. In consequence, his observations are unsystematic and fragmentary.

The present study, though in its turn patently incomplete, has been carried out on a larger series of monkeys over a longer period of time against the richer background of current concepts of function in the nervous system. It has brought out features of experimental pyramidal lesion previously unappreciated ; most notably: that the ensuing paresis is flaccid, or better, hypotonic in character—a reversal of prevalent clinical concept. More than this, the negative impress of pyramidal function yielded by the defect of pyramidal lesion has both enlarged and delimited the known domain of action of the corticospinal tract, and has shown how this activity operates with respect to time. Likewise, the positive picture of extrapyramidal function obtained after both pyramidal tracts are cut, has clarified space and time dimensions in that field of activity. The object of this study has been, less to establish the symptomatology of pyramidal lesion, than, through analysis of such symptomatology, to arrive at a better understanding of the function of the pyramidal system, and of the co-operation of pyramidal and extrapyramidal components in the total complex of projected cortical motor function.

Procedure

To section the medullary pyramids an approach is made from the anterior mid-line of the neck, passing to the right of the pharynx and larynx, detaching the longus capitis muscles from the basi-occiput, making a hole in this bone, and a cruciate slit in the dura. The basilar artery is then freed in the pia and displaced to one side, thus exposing the pyramid to be cut. The section is made by inserting a dull iridectomy knife down the median sulcus, turning it to face the pyramid, and bringing it out laterally by an arc at the sulcus which delimits the lateral border. The knife is then inserted at this lateral sulcus and brought medially, to ensure that all the fibres are cut. The pyramid has sufficient integrity as a fibre strand so that with a little experience, completeness of the lesion can be felt, or, by everting the cut ends, seen. For a bilateral section, the basilar artery is then shifted to the opposite side, and the procedure repeated on the intact pyramid. When well executed the operation is practically bloodless throughout, but bleeding

from the dural sinuses is easily controlled and has no untoward consequences. Opening the basilar artery or any of its large branches has been found incompatible with survival. Closure is effected by laying the dura and deeper structures in place so far as possible, suturing only the subcutaneous tissue and skin. The ether anæsthetic is administered through a two-way tube in the trachea, atropine being given first.

The trapezoid body is the level of election for pyramid section because of the protection thus afforded by this portion of the acoustic system to deeper lying ascending and descending systems whose injury would complicate the results. Occasionally an unfavourable arrangement of the branches of the basilar artery has made it necessary to place the lesion lower, in the interval between the trapezoid body and the head of the olive, but in only one case has it been placed below this level, and in no case higher than the trapezoid body.

The material of this study has been the common rhesus monkey (*Macaca mulatta*), adult or adolescent. This paper will analyse in detail only the condition following complete unilateral or bilateral pyramidal lesion, and one instance of unilateral lesion in conjunction with bilateral ablation of cortical Areas 4 and 6 of Brodmann. Nevertheless, a series of 2 accidentally and 3 deliberately incomplete pyramid sections has also contributed by demonstrating the fundamental difference between completeness and incompleteness with this lesion. Furthermore, another series of pyramid sections in infant monkeys will be frequently cited as confirming, and thus giving general validity to observations presenting only infrequently, or in a single animal of the adult series. This will apply particularly to consideration of residual function which is very much less depressed by pyramidal lesion in infancy than in adult life.

All the monkeys were fixed after death by intra-aortic injection either of Müller's fluid or of 10 per cent. formalin, following perfusion with physiological salt solution. The brain and cord were removed and carefully examined grossly. In the more important members of the series brain-stem and cord were examined microscopically by Marchi or Weigert technique as indicated. The cerebral cortex will be examined by Nissl technique later.

Unilateral Pyramidal Lesion

Section of one pyramidal tract at the medullary level, if properly done, is well borne by the monkey. An hour or so after completion of the operation the animal can usually sit up; after twenty-four hours it begins to take food, and by the end of a week it is fully recovered except for the specific results of the lesion. Animals surviving more than one month were turned loose in a large outdoor paddock where they competed successfully with other monkeys, some of them normal. Ten complete unilateral pyramid sections surviving operation two days to thirty-two months have been available for study. One monkey died on the third post-operative day of undetermined cause, probably medullary œdema; four others were used, after brief observation, for electrical stimulation of the cerebral cortex; and five animals have yielded the bulk of the data to be described. Of

these, two were killed after two weeks for Marchi material; one was killed after three weeks because of the sudden onset three days after operation of nystagmus and other adventitious symptoms; one, a vigorous male, was killed in a fight eight months after operation, while the last was kept for thirty-two months during which time she delivered and cared for a healthy infant. These five animals have been examined microscopically. Although the pyramid section was in every case complete, in only two cases was it just complete and no more. Cranial nerve involvements and other variably presenting disorders will be described in conjunction with anatomical study of the brain-stem where they may be correlated with variation in the level and extent of the lesions. The consistently presenting disorders are considered to constitute the specific results of interruption of one corticospinal tract.

In contrast with the slight general disorder following section of one pyramidal tract, the specific results of the lesion are grave and enduring. With the exception of muscular atrophy, they are all in evidence immediately the animal has recovered from the anæsthetic, and persist, with little amelioration, for as long as the animal survives, in one case for almost three years. Furthermore, the condition shows no variation from animal to animal except as superficially introduced by differences in temperament. This stability and invariance of the results of pyramidal lesion greatly facilitate analysis and description of the condition. Briefly stated, the disorder consists in hypotonic paresis[1] of the opposite side of the body, affecting all somatic function, though not equally, and some visceral function. Its outstanding features are diminished muscle tone; diminished cutaneous reflexes; slow, full tendon reflexes restricted to the muscle stimulated; lowered skin temperature; defective initiation and execution of all performance by skeletal musculature with elimination of non-stereotyped components, and elimination of all discrete usage of the digits. In the realm of somatic motor function, the condition is unquestionably entirely one of deficient function, without phenomena of release. The vasomotor condition is ambiguous, but probably similar.

Skeletal muscle tone.—Tone is gravely deficient in all the skeletal musculature of the side of the body opposite the lesion with the exception of neck, back and thorax musculature, and even these may be somewhat affected. The hypotonia is visible and palpable in all positions and at

[1] The terms "hypotonic" and "paresis" are used in preference to "flaccid" and "paralysis" as connoting a less grave loss of tone on the one hand, and of usage or movement on the other. The distinction in the author's mind is purely quantitative, but useful.

all times in the waking state, although influenced by posture, activity and state of mind. It has not been possible to examine the sleeping state. Sitting quietly, the paretic extremities hang lower and looser than the normal; indeed, the relaxation of the shoulder muscles is such that the arm sags loosely forward across the body (fig. 3, p. 53). Held in the air or supine, positions in which normal tone is increased in the animal's resentment, the flabby behaviour of the affected extremities under gravity is strikingly apparent. During the first few weeks even the half of the abdomen may be observed to sag, and the abdominal wall between iliac crest and lowest rib to be less tautly drawn in. The hypotonia is demonstrable as diminished resistance to passive movement at all joints and in all directions, and as diminished resistance to palpation of the abdomen. Deliberate voluntary resistance to the passive movement further enhances the difference between the sides, although violent struggling tends to obscure it. In testing the extremities it matters not whether a positive supporting reaction be elicited or avoided: the difference is equally demonstrable. There is, in fact, no condition of the animal except perhaps sleep in which the difference is not conspicuous.

The hypotonia by no means affects all parts of the skeletal musculature equally, however. In general, the lower extremity is more hypotonic than the upper, and both more so than the trunk. Within an extremity the musculature which attaches it to the trunk is more hypotonic than the distal musculature, especially in the arm. At any specific time posture influences the condition. Thus sitting in a chair, all the muscles of the shoulder are about equally and very gravely affected, but from shoulder to digits, the extensors are more hypotonic than the flexors, and the finger abductors more so than the adductors. In the leg, flexors and extensors of the knee are about equally slack, but the dorsiflexors of the foot, and in the foot, the plantar-flexors and adductors of the digits are more severely affected than their antagonists. These differences determine the resting position of parts. When standing, and to a lesser extent when supported prone with the extremities dependent, tone is increased in the antigravity muscles so that the previously weaker plantar-flexors of the toes and extensors of the arm may become stronger than their antagonists, although compared with the normal side their tone is still deficient. Yet the retractors at the hip are still so weak relatively to the protractors that the heel is often prevented from resting on the floor. In the standing posture the tail may deviate to the normal side, and sitting or standing there may be a suggestion of concavity of the back to this side also.

Although the quantity and distribution of tone in both affected and

normal sides are influenced by position in space, differing in each of the prime positions (prone, supine, sitting, standing, lying on one side or the other), lesser postural variations of a passive character are without detectable influence. Tonic neck and labyrinthine reflexes were assiduously sought because of their occurrence in hemiplegic man, without vestige of result. Active turning of the head to the affected side beyond about 60 degrees from the mid-frontal plane involves movement of the entire body from head to tail including the lateral pair of extremities, which is not necessarily the case with turning to the normal side. This phenomenon is not, however, in the category of tonic neck reflexes, but demonstrates one characteristic of the residual extrapyramidal activity, namely, its widespread organization.

Reflexes.—Unilateral pyramidal lesion impairs the phasic reflexes of the opposite side as it does reflex tone. In general, threshold is raised; scope is limited; and the reflexes are sluggish and weak. Superficial reflexes are more severely affected than deep. Thus the abdominal[1] and cremasteric reflexes are practically abolished initially, while both these and the reaction to pin-prick are enduringly reduced over the entire half of the body from neck to toes including the perineum. Commonly the normal side reacts before the side affected on stimulation of the latter. As Fulton and Kellar (1932) have shown, the macaque has no pathological sign of Babinski. Plantar stimulation, stroke, pinch or prick, may evoke either dorsiflexion or plantar-flexion of the digits with fanning or adduction, depending on the site and mode of stimulation, on the position of the extremity, and on the animal's actual or intended activity at the moment. Similar palmar stimulation almost always evokes flexion and adduction. However, in a quiet animal accustomed to the test, the usual reaction in both hand and foot is flexion and adduction, followed by dorsiflexion, fanning and withdrawal if the stimulus is strong. This pattern, and the predominance of this pattern, are quite undisturbed by unilateral pyramidal lesion except that threshold is raised both for the initial reaction and for the subsequent withdrawal, and more so on the sole than on the palm. On the sole, stroke may be no longer an adequate stimulus.

The deep reflexes routinely examined were: in the arm; biceps, triceps, periosteo-radial and finger-jerks; in the leg; hamstring tendon reflex, knee-jerk, Achilles tendon reflex and toe-jerks; in the abdomen, the reflex

[1] In the adult macaque, though not in the infant, stroke is rarely an adequate stimulus for the abdominal reflex, and pin-prick must be used. The younger the monkey, the greater is the likelihood of obtaining the stroke reaction.

contraction to deep pressure suddenly applied. After unilateral pyramidal lesion all the deep reflexes are still obtained consistently on both sides except the toe-jerks. On the side opposite the lesion, however, they are raised in threshold and altered in character. Instead of the normal quick reflex, quickly checked by contraction in the antagonists, and, in the monkey, usually irradiating to muscles more proximally located (in contradistinction to the adult chimpanzee and man), the reflexes become slow, full because unchecked, and restricted to the segment stimulated except for the ankle-jerk which still recruits the thigh flexors.

With the deep reflexes, as with muscle tone, the position of the animal, and of the part, during examination influence the result. In the sitting posture the difference between the two sides is slight in the arms but great in the legs, whereas in the supine posture, if the animal will relax in this position, the difference betwen the arms becomes nearly as great as between the legs; and both are maximal. The prone position with the extremities dependent is on the whole least satisfactory for reflex examination because of the animal's resistance. However, it usually augments tone in the flexors of the digits sufficiently to permit of obtaining toe- as well as finger-jerks, thus completing the series of deep reflexes. Also it permits examination of many deep reflexes of the back, which are only slightly if at all enfeebled by unilateral pyramidal lesion.

The difference between the two sides is best studied at a maximum in the knee-jerk, with the animal sitting, the thigh supported, and the lower leg and foot dependent. The knee-jerk is then very slow and full, and passively pendular because of the failure both of check contraction in the antagonistic flexors, and of adaptation reflexes in the quadriceps itself. There is not the slightest suggestion of the tonic prolongation characteristic of spasticity, or of after-discharge in any form. The motor locus of the reflex impairment is strikingly shown in respect to the crossed adduction which accompanies the knee-jerk in a lively, uninhibited monkey, especially from a tap slightly on the medial side of the patella. A patellar tap on the paretic side will cause the normal leg to adduct, but not the reverse. In fact, a stimulus on the affected side which is below threshold for that knee-jerk, may still excite crossed adduction on the normal side. Ipsilateral adduction may accompany either knee-jerk, but is very much more frequent on the normal side.

Although the reflexes are in general gravely weakened by pyramidal lesion, they are remarkably stable in their new state. Thus they are little affected by changing moods of alertness or boredom, tension or relaxation, which can augment or virtually eliminate the normal reflexes. This

inaccessibility of the paretic reflexes is at a maximum in the curious, stubborn passivity which all monkeys may assume at times, and which certain monkeys affect habitually. In this state both superficial and deep reflexes may be virtually inelicitable for long periods of time on the normal side, and before operation, on both sides ; but on the paretic side the process of restraint, or exclusion, which seems to be accomplished by fixing the muscle in slight continuous contraction, is not effective.

Clonus was never obtained by any procedure in any part affected by the lesion, nor any suggestion of the " clasp-knife " phenomenon in resistance to passive movement. Moreover, the clonus which may be obtained from time to time in quite normal, but tense monkeys, was abolished opposite the lesion in two members of the series, while persisting as an occasional occurrence on the normal side.

Vasomotor activity.—After unilateral pyramidal lesion the opposite hand and foot are almost always palpably cooler than those of the normal side except in hot weather or after strenuous exercise. This difference is exaggerated by bringing the animal from the cold to a warm room because the normal hand and foot rapidly warm up while the affected side reacts more slowly. The discrepancy is greatest in aggressive, unfatigued animals, and is diminished by fatigue, by emotional and physical relaxation and somnolence, and in the state of stubborn passivity. The basic difference between the two sides persists with passage of time after operation, even of years, although familiarity with observer and procedure tends to minimize certain aspects in friendly animals. The difference is greatest on the hands and feet, but is appreciable, by the use of more delicate tests than palpation, on more proximal parts, especially in the axilla and groin. Here also, the side opposite the lesion is the cooler. On very hot days, however, or after strenuous exercise, both sides may be very nearly equally warm and pink, or the paretic side may even be the warmer.

To use skin temperature as an index of vasomotor activity requires control and simplification of the conditions of examination, and the size and constancy of the differences between the two sides permit of this. Change in environmental temperature was avoided because of the difficulty of interpretation if both the heat supplied to the skin and the rate of heat loss be altered. Physical activity was reduced to a minimum, and disturbing psychic and emotional factors eliminated so far as possible except when they were under specific investigation. As worked out finally for routine examination, the animal was brought to the room in which the test was to be conducted the day before. At the time, he was caught by a collar and chain and rapidly strapped in a chair, with a minimum

of physical exertion and a probable maximum of emotional excitement. Using at first thermometers, later a thermopile sensitive to tenths of a degree centigrade (Tycos dermatherm), readings were made of skin temperature on both hands and both feet, and occasionally elsewhere. Differences in skin temperature of homologous parts met with in these tests and considered significant ranged from 0·5 to 5° C. Sometimes the animals were allowed to rest in the chair for an hour before the first reading was taken, but more frequently readings commenced at once and continued for from one to four hours. In the first case the records represent the closest approximation possible in the unco-operative adult monkey, to

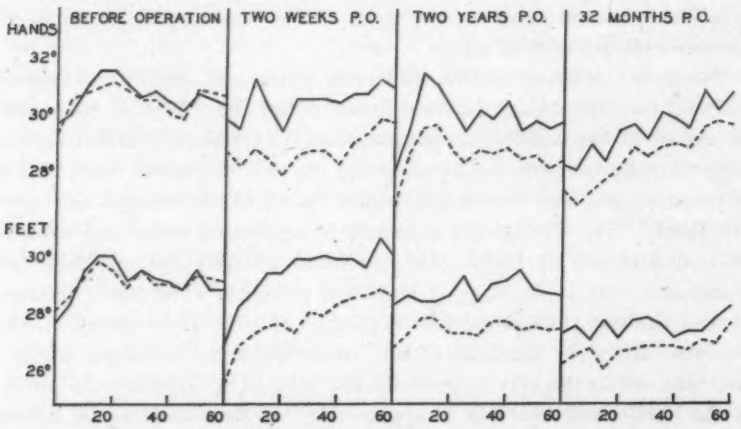


FIG. 1.—Records of "basal" skin temperature on hands and feet, obtained before and after unilateral pyramidal lesion from the monkey whose lesion is shown in figs. 7 to 10. Solid line: normal right side; broken line: paretic left side. Temperature in degrees centigrade. Time in minutes. The records were taken after an hour's rest, and with minimal disturbance.

a basal vasomotor condition. In the second case the first hour's readings record recovery from what is probably the monkey's strongest vasoconstrictor reflex, that to fear-rage, and establish a control for the specific tests. These involved immersion of both feet for one hour in ice-water, followed by one hour at 47° to 49° C, readings being taken from the hands. During the fourth hour another set of control readings was obtained. Room temperature was kept approximately constant throughout any one examination usually at some figure between 24° and 28° C. Readings were taken in rapid succession from the centre of the palm, and from the space between 1st and 2nd digits on the foot, in the order left hand, right hand, left

foot, right foot, and alternatively in the reverse order. The series of readings may be completed in less than half a minute with the dermatherm, and in about one minute with thermometers, but readings were never taken at less than minute intervals, and usually at 2·5 or 5 minute intervals to reduce the annoyance to the animal. On the whole, the general trend during the course of an hour is the significant result, and moment to moment fluctuations are of less import.

The effect of pyramidal lesion on skin temperature and vasomotor control is best shown in actual records. Fig. 1 presents records obtained before operation, and two weeks, two years and thirty-two months after operation from the animal whose lesion is shown in figs. 7 to 10, under

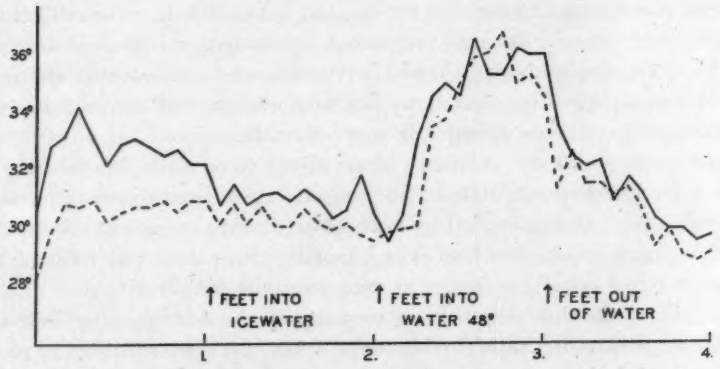


FIG. 2.—Record of skin temperature taken on the same monkey thirty-two months after unilateral pyramidal lesion. Solid line: normal right hand; broken line: paretic left hand. Temperature in degrees centigrade. Time in hours.

"basal" conditions. They show unequivocally the enduringly lower temperature on the paretic side under such circumstances. Fig. 2 presents a four-hour record obtained from this same animal thirty-two months after operation. This record shows, besides the generally lower temperature on the side affected by the lesion, and an occasional momentary reversal of this condition, the effect of the lesion in delaying the onset and reducing the vigour of vasomotor reactions of several sorts, both dilator and constrictor. When one or two minute intervals were used the smallest and briefest variations are missing altogether.

An aspect of some records not shown in these figures, which appears only if minimal time elapsed before the first reading was obtained, is that the normal hand may have at the start (that is, shortly after the climax

of the constrictor reaction to being caught), a lower skin temperature than the affected hand. Not infrequently a similar condition is palpable in aggressive monkeys, when some other phase of examination is violently resented. The vasoconstriction to cold is feeble by comparison, and fails to bring out this apparent weakness of the constrictor reaction. On the other hand, at the extreme of the dilator reaction to warmth, which is much more vigorous than the constrictor reaction to cold, the affected extremity sometimes registers, briefly, a higher temperature than the normal, recalling the spontaneously higher temperatures met with on hot days. Barely suggested in the series of adults, as in fig. 2, this has been a common occurrence in monkeys operated on in infancy. Relaxation and lack of apprehension seem to favour it. Possibly the phenomenon may be viewed as analogous to the slow full tendon-jerks ; that is, as vasodilatation reaching an extreme because unchecked by antagonistic vasoconstriction.

None of the monkeys showed any trace of hemi-œdema, not even immediately following operation, nor any evidence of trophic disorder in skin, nails or bones months or years thereafter.

Sudomotor activity.—Cursory observations were made on sweating in two varieties of circumstance: in response to a psychogenic stimulus: apprehension ; and as evoked by heat, either during immersion of the feet in hot water or on very hot days. Usually the palms and soles of the two sides feel equally moist. On rare occasions, however, a difference is detectable in the direction of lesser sweating on the side opposite the lesion. Likewise, when the animal is brought from the cold to a warm room, moisture is sometimes perceptible sooner on the normal side even though later both sides appear to be sweating equally. No distinction can be made between psychogenic and thermal stimulation in relation to this trifling and unpredictable inequality.

Pilomotor activity.—Erection of hair was similarly studied with psychogenic and thermal excitation ; as part of the threat reaction, when the hair of the head, upper back and arms is erected ; and during immersion of the feet in cold water, when pilo-erection is fairly general over the body. In neither circumstance was a difference detectable between the two sides of the body in the extent, vigour, or timing of pilomotor activity.

Shivering.—The tests in which the feet were immersed for one hour in ice-water gave frequent and prolonged opportunity to examine shivering. So far as inspection and palpation reveal, the two sides engage in this activity equally vigorously. Certainly, there is no overt enfeeblement of this activity such as might even be expected to accompany the muscular

hypotonia. Nor, on the contrary, is there anything in the shivering of these animals, compared after operation and before, or compared with the shivering of normal monkeys in similar circumstances, to suggest a general over-activity of the shivering mechanism such as Aring (1935) has described in consequence of partial or complete, unilateral or bilateral ablation of the motor area (Brodmann's Area 4) in monkeys.

General usage and specific performances.—The most conspicuous result of unilateral pyramidal lesion in the monkey is diminished general usage and loss of initiative in the opposite extremities. The loss of initiative is grave, but not complete. When both sides are free to act, initiative of almost every sort is delegated to the normal side, but if the normal side is restrained the affected side can, with sufficiently strong excitation, be brought to act. The effect on usage is complex, attacking specific performances differently in their different components. In general, least stereotyped components are eliminated while more stereotyped survive. Thus all discrete usage of the digits disappears, together with the corrective movements for unusual postures, and the ability to take accurate aim, or to modify movement in the course of execution. In contrast, the stereotyped components of activity function well. Though weakened and demonstrably high in threshold, they are still useful to the animal. Bilaterally integrated performances suffer on the whole less than those executed by one side alone, or by one extremity alone. In necessarily bilateral performances such as progression and climbing, the normal side leads off. Performances executed solely by one side, or by one extremity, are usually attempted only by the good side. But experience reinforces the basic defect here, because during the first few post-operative weeks animals may occasionally be observed making postural preparations for an act (those for grooming and scratching are unmistakable), obviously intent on the act, unable to execute it, and finally giving up, often with a physical movement of annoyance, shrugging the shoulders and turning away. After a time such frustrated attempts cease, and the animal uses his normal side more and more exclusively.

By elimination of non-stereotyped components the activity of the paretic side is reduced to a limited number of stereotyped performances. Those most in use are: the assumption and maintenance of posture, including righting; orientation of the body as a whole to external objectives; progression; reaching-grasping; scratching; striking and kicking. Divested of accuracy and of modifiability in the course of execution, in general weakened and sometimes even tremulous, these extrapyramidal activities are employed by the animal with unilateral lesion only when they are indis-

pensable as in the case of maintenance of posture or bilaterally organized progression, or when the good side is prevented from acting, or with a strong emotional drive as in fighting. Moreover, any separate employment of the affected arm and hand other than for support gives the impression of requiring enormous effort, and is never long continued. But obviously the taxing effort is not muscular for the work done is slight indeed, scarcely to be compared with the effort of running or jumping around a large cage in which this arm participates easily. Furthermore, if, after activity of this kind can no longer be elicited, the animal is incited to anger, muscular efforts may then be put forth by the affected extremities little if at all weaker than on the normal side. It appears, therefore, that the effort and the fatigue are largely one of the will.

Postural activity, progression, placing and hopping.—Considered as a whole, the complex of postural, progressive and corrective activity illustrates well the nature of the pyramidal defect. The large patterns of activity are intact both for the maintenance of posture by tonic innervation and for the assumption or change of posture by movement, but these activities are gravely disordered. Initiative is below normal and threshold is raised. The tonic innervations or movements called forth are feeble, and poorly sustained. Non-stereotyped components in the form of aim, adjustment and terminal correction are eliminated, leaving the activity which survives exceedingly stereotyped. Yet in spite of these defects postural activity, alone or with progression, is still the largest requirement made of the affected extremities after unilateral pyramidal lesion.

Postural activity is cast in the monkey in two forms, the tonic extension and fixation which converts a limb into a rigid support for standing, and the grasp and suspension introduced by the arboreal mode of life. Three well-known postural reactions have been examined. These were: (1) the positive supporting reaction, obtained when a hand or foot is brought to rest on a solid surface with all or part of the body's weight bearing on it; (2) the reaction obtained when an extremity which is supporting the body is withdrawn from contact with the supporting surface, the animal being slowly lifted; (3) the reaction obtained in free extremities when an animal is dropped rapidly through space. The first two of these reactions are largely excited in the extremity responding, the first by proprioceptive and cutaneous stimulation; the second by cutaneous, whereas the third is vestibular in origin. The animal may be blindfolded to simplify the conditions of examination. All three of these are primarily terrestrial adaptations.

The sudden requirement of a normal extremity to support the body-

weight produces: first passive flexion, checked at once by active extension. This extension merely straightens the arm, but brings the heel momentarily off the surface. For a few days after operation the paretic arm and leg, tested singly, may fail to support the body-weight in a positive supporting reaction; and enduringly, extension is delayed and weakened so that the passive flexion is only slowly checked. The weakness of postural extension may be readily gauged by comparison with the normal fellow, if additional pressure is brought to bear on the supporting extremity by pressing on the animal's back. If both arms or both legs are tested together, the performance of the paretic side may be improved somewhat, but not to equal the normal. On testing both legs together, the tail deviates in elevation to the normal side.

The dropping reaction further illustrates the weakness of postural extension in the paretic extremities. During the course through the air arm and leg are extended and abducted, even excessively in a floppy fashion, and the digits fan, showing that the vestibular reaction survives. But if strength be tested by bringing the body-weight to rest on one extremity, or on two homologous extremities, a paretic extremity yields more under the burden, and the animal stumbles or scrambles to the standing posture instead of rising to it as if on a spring. This latter reaction is, of course, the positive supporting reaction again.

The reaction to loss of support incorporates both extensor and flexor activity. Normally, if support is slowly withdrawn from the standing animal, either by lifting the animal or by dropping the support, a supporting extremity extends to the utmost to maintain contact as long as possible. This is shown in the normal leg in fig. 6. Immediately the contact is broken, however, the extremity flexes. In paretic extremities both the extension (fig. 6) and the after-flexion are curtailed, or missing altogether.

The grasp and suspension developed in arboreal adaptation are less standardized, and less easily examined. A hanging test, using a wood or metal rod ½ or ¾ in. in diameter, may be applied to each extremity singly, the others being tied and the animal blindfolded. The normal adult monkey cannot support his body-weight even momentarily by grasping the bar with one foot alone, but he can, and often will, hang by one hand for a measurable period of time before letting go, especially while the procedure is still unfamiliar. Unilateral pyramidal lesion so weakens the arm that this, too, becomes impossible. Nevertheless, if the animal is supported so as to reduce the burden on the extremity, the basic pattern of grasp and suspension is demonstrably intact. A better idea of

this total function may be obtained by observing the monkey loose in a large cage. The burden of suspension is then seen to fall on the normal side, but with the paretic side assisting. The fingers and toes of the affected side grasp the mesh or bars weakly and imperfectly, the toes often not at all, handicapped by the difficulties of engagement and disengagement to be described later.

Progression, like posture, assumes in the monkey two forms, adapted respectively, to terrestrial and to arboreal life. The first of these, in either the diagonal pattern of walking and running or the symmetrical pattern of the gallop, is the best preserved of the more complicated somatic motor performances after unilateral pyramidal lesion. Yet it is far from intact. The rhythm of diagonal progression is disordered by delayed participation of the affected extremities in every cycle. The centre of gravity is displaced toward the normal side, and the animals develop a practice of circumducting the paretic extremities, throwing them forward, as it were, by the use of the less paretic axial musculature. When moving slowly, the fingers and toes often drag. When moving fast, on the contrary, the affected leg is excessively protracted in a loose way which characterizes many movements vigorously executed by the paretic extremities. By six months after operation the animals develop a habit of covering even short distances at low speed by a succession of hops or bounds in which the entire thrust is made by the normal leg, with the arms serving as props and the paretic leg either propping, or flexed continuously out of the way. This appears to be an adaptation of the gallop pattern ordinarily used only at high speed. The tendency to omit using the affected leg reaches an extreme in shifting movements of the sitting animal, as in pursuit of food, when the good leg propels the animal along, the other dragging. Initiative in progression is usually delegated to the normal side, the only consistent exception being in the act of stepping up to a higher level in which the task of supporting the body-weight is given to the normal side, the affected side making the first step up. Here, apparently, normal strength is at a higher premium than normal initiative.

In arboreal progression, as in terrestrial, the basic pattern is intact: reaching-grasping in conjunction with a leap; but again performance is defective. In jumping, the extremities again over-act. Extension is abrupt and abduction excessive, while the digits hyperextend at the metacarpophalangeal joints and flex at the interphalangeal in the claw-hand posture of infancy. Landing is without spring. Frequently, when only a small shift in position is being made, the paretic extremities may not be employed at all, or even replaced in conformity with the new position, but are left, as it were, passively behind.

Placing and hopping.—After unilateral pyramidal lesion the positions habitually assumed by the affected extremities are largely determined by the animal's last action, and by gravity. Thus as the animal halts and sits after moving, the affected foot is often left in abduction or hanging off a shelf, whereas the normal is neatly placed under him. Similarly, the arm hangs dependent across the body unless the normal hand takes hold of, and folds the affected hand in—a habit the animals acquire in time. Such abnormal positions, in themselves largely passive, expose a defect in the class of adjustive and corrective activities called placing and hopping which are normally integrated with postural, or progressive, or other activity, on which they confer finish. The tests devised for these activities, however, dissociate them from such context, and make them little stereotyped reactions to particular situations, preferably affecting one extremity at a time. As such, the reactions are gravely and permanently weakened by pyramidal lesion, and in large part abolished.

The placing reactions examined were four: (1) the reaction to contact with the fingers or toes of the extremity being tested; (2) in the failure of contact reaction, the reaction to contact plus proprioceptive stimulation by passive movement of the extremity being tested; (3) the reaction to contact of the chin with a table or other solid surface (for these three tests the animals were blindfolded); (4) the visual placing reaction as the animal is brought toward a table with the eyes open. The extremities were tested both singly and in homologous pairs. The positive placing reaction consists in a smoothly executed sequence of flexion and extension with accessory components of protraction, or retraction, abduction or adduction, inversion or eversion, to suit particular circumstances. The toes or fingers make contact with the support first. Alternatively, particularly with visual stimulation, the animal reaches for and grasps the edge of the support offered. In certain individuals, or under certain circumstances a negative, or avoiding reaction, replaces the positive, but animals of persistently negative character were largely excluded by pre-operative examination.

Pyramidal lesion abolishes the contact reactions, whether of the extremity being tested or of the chin, completely and permanently. If a pair of homologous extremities are free and contact is made with the affected extremity, the normal frequently places although not itself stimulated, while the paretic extremity does not even follow. The occurrence of this crossed contact placing reaction, and the elimination together of both the chin contact and hand or foot contact reactions prove that the defect is motor, and not the result of damage to the ascending sensory systems in their course through the medulla.

The proprioceptive and visual reactions are suppressed initially for a variable period, and never subsequently make anything but the most fragmentary reappearance, usually only when the animal is excited and on the verge of struggling. If the animal is tired or ill, or the weather hot, they are almost always undemonstrable. Proprioceptive placement cannot be compared between the two sides as to threshold because the normal side reacts to the initial contact, but the enormously higher threshold of visual placement on the side affected by pyramidal lesion is obvious. Visual placing is usually better in the paretic arm than leg ; proprioceptive placing, the reverse. Figs. 4 and 5 illustrate these defects in arm and leg.

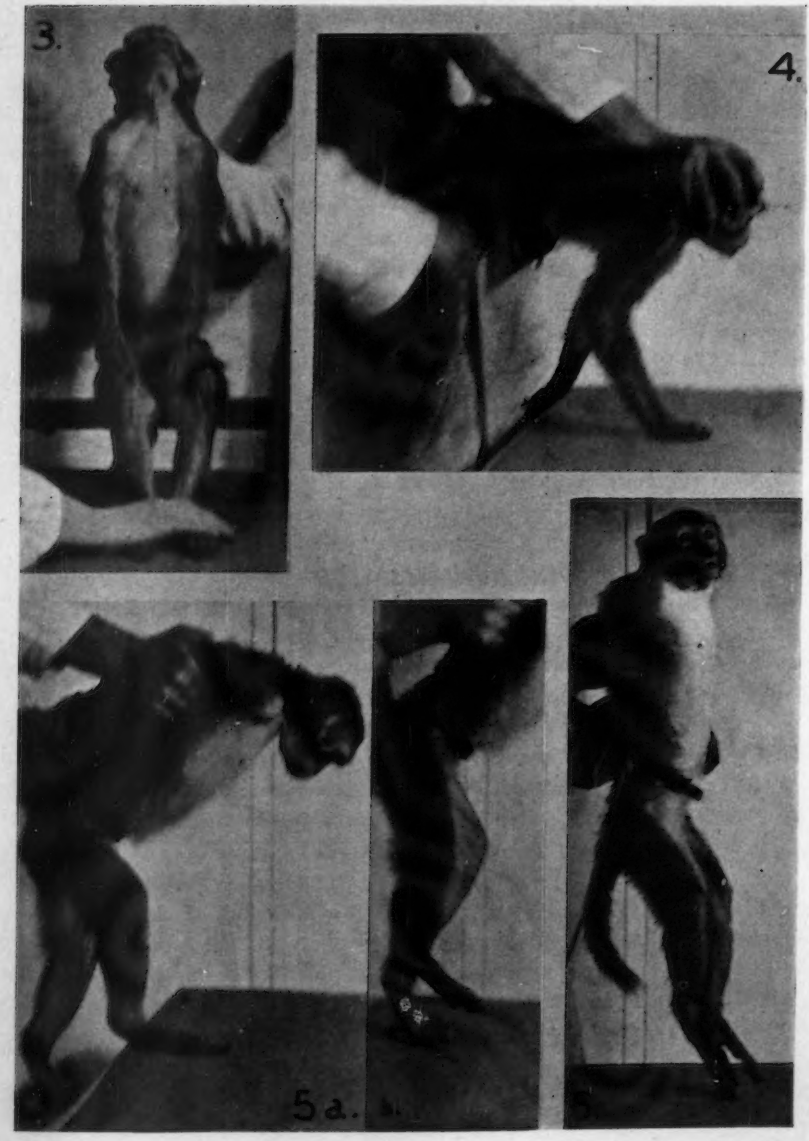
Another placing reaction, which came under observation more than all these together, might be called the sitting reaction. With the animal in the examining chair, the normal arm and leg place on any available object, the foot grasping the paretic ankle as a last resort, and they replace as often as the placement is disturbed. In contrast, the paretic arm and leg hang dependent and unplaced for the duration of the examination—sometimes for hours. Furthermore, passive displacement of these extremities is not resisted even though the displacement is extreme, unless a general struggle ensues.

The hopping reactions were tested in the blindfolded animal by obtaining a positive supporting reaction in an extremity and then displacing the animal's body so as to adduct or abduct, protract or retract this extremity, maintaining the original orientation of the head in space. The stimulation is thus largely kinæsthetic. A positive reaction replaces the extremity under the animal's centre of gravity. Usually, instead of single reactions, the number of "hops" in a 7 ft. length of continuous displacement was determined, thus giving a quantitative aspect to the results.

Pyramidal lesion affects the hopping reactions as it does proprioceptive placing. After a period of complete suppression the reactions are again occasionally elicited, especially when the animal is excited and inclined to struggle. The recovery is better in the leg than in the arm where the correction of abduction never returns. But even in the leg the number of steps to the standard interval rarely approximates to half the normal, and performance is ragged, while the reaction fatigues so easily that after making two or three hops the leg usually commences to drag. Speeding up the rate of displacement improves the performance.

Tested in conjunction with the corresponding normal extremity, both the proprioceptive and visual placing reactions and the hopping reactions are usually initially excitable in a paretic extremity, though easily fatigued. On continuing the test, the paretic extremity may either continue to follow

PLATE I.



For descriptions see p. 90.

the normal in a delayed and ragged performance, or it may begin to drag after a few steps. Contact placing is not brought out in this fashion.

Exploratory, acquisitive and other activities, largely digital.—The monkey's digital performances may be divided into two categories: those in which the digits operate together as in scratching and brushing movements, or in grasping, or as integrated in larger performances such as placing, and progression; and those in which the digits are used separately as in the opposition of thumb and index to pick up small objects, or in fine manipulation of objects, or in separation of one digit from the others to inspect or clean it. The latter group of reactions is most highly developed in the hand, while the former occupy hand and foot about equally. Pyramidal lesion discriminates sharply between these two types of activity. The first is slowed and weakened; aim and execution are impaired; threshold is raised, often virtually eliminating the performance, but when the threshold is surmounted, the pattern is not basically altered. Only two common performances using the hand as a fist, namely emptying the food pouch and rubbing the eye, have never been observed in the paretic arm. On the other hand, all discrete usage of the digits is utterly and permanently eliminated, without surmountable threshold in any case.

The grooming performance illustrates this discrimination. Grooming consists of two acts: a brushing or raking act in which the digits are used together, first rhythmically, and then steadily, to hold the hair back; and a picking or plucking act, opposing thumb and index, with the other fingers flexed into the palm. These may be executed in variable sequence by one or both hands, without preference between the sides as in the case of handedness in man. Only the longest surviving monkey recovered any part of this performance. In the thirteenth post-operative month this animal reestablished the raking or brushing act, but neither then nor thereafter was the plucking act even suggested, unless by certain curious intent pauses in the brushing, after which the animal usually shrugged her shoulders and turned away, or fell to using the normal side, or to scratching. The brushing performance remained slow, clumsy, poorly aimed in that it took place in the air as often as among the hairs, and easily inhibited by extraneous disturbance. It was applied only to grooming the normal arm and hand—that is, in a field not accessible to the latter. Similar abbreviated grooming has been observed in all infant monkeys with pyramidal lesions, developing together with normal grooming toward the end of the first half year.

The act of grasping objects, for example food, illustrates again the discrimination of pyramidal lesion. The normal hand takes over the full

burden of routine feeding, the paretic hand never being employed when both are free. Yet a residual capacity of the affected hand is easily demonstrated in tractable animals, even as early as the day after operation, by holding or tying up the normal hand and then offering food. Instead of the normal movement which culminates in the opposition of thumb and index to pick up small objects, and of thumb and all the fingers for large objects, with adaptation to circumstances of the greatest diversity, the residual movement of the paretic arm is a highly stereotyped reaching-grasping act involving the entire body-half, similar to the reaching-grasping act of the newborn monkey Like this latter, it is characterized by excessive abduction and limited protraction. The hand is brought down on the object in half pronation and scoops it into the ulnar side of the hand, unless, as frequently happens, the fist closes before reaching the object. When this happens, the impasse is resolved either by a series of rhythmic clawing movements, or more frequently, by bringing the arm back in adduction, flexion and supination, and repeating the whole sequence. This latter movement also serves to bring the object, if seized, back within range of the mouth. The transfer to the mouth is effected by bringing the mouth to the hand where the lips then remove the food from between the fingers which themselves do not open. The act is quite incapable of modification so as to take food from between the observer's fingers, or from any except an unobstructed surface. It is unsuccessful with small objects such as kernels of grain. Aim is achieved by orientating the entire body, although if this be prevented, some latitude is still possible. The reaction is stereotyped to the degree that if the object be shifted in the course of execution, the movement is completed as aimed, and then, when unsuccessful, a new body orientation is made, and a new movement initiated.

This performance vividly illustrates the raised threshold of residual extrapyramidal activity, for only if the animal is very hungry or the food particularly desirable will the affected hand be employed to obtain it. Thus the animal will reach for candy but not for potato, even when potato is an adequate stimulus for the normal side. Correspondingly, the performance is also easily fatigued, for if the monkey is permitted to reach for the candy alternately with the paretic, and with the normal hand, while being prevented by a wire mask over his head from eating it and thus diminishing its value as a stimulus, the performance continues almost indefinitely on the good side but quickly ceases on the paretic side.

Climbing on a fairly close wire mesh brings out the defect in digital usage in the foot as well as in the hand. On a mesh which admits the digits easily, the normal hand will usually engage all five fingers neatly,

and the foot, all the toes except the first at each resting position, while with the affected side engagement is hit or miss. The animal perseveres with the hand, clawing rhythmically at the mesh until some of the fingers engage, but quite commonly none of the toes engages, and the body-weight is supported and lifted merely by pressure of the sole against the mesh. The difficulty in climbing proceeds from loss of slight adjustments by the digits themselves, largely adduction and abduction, which would bring them to one side or the other of an impeding wire and permit entry; of similar movements at the wrist of lateral and medial deviation; and of movements at the shoulder shifting the whole extremity. The grasping movement in which the digits operate together is intact.

Releasing grasp.—Parallel with and complementary to difficulty the animal has in taking hold of objects, is a difficulty in letting go. Under ordinary circumstances this does not obtrude in the adult monkey. The paretic hand takes hold only in climbing, and in climbing the difficulty presents as passivity only, the weakness of the grasp being such that the digits slip under the slightest strain. The difficulty can be brought out, however, by tying up the normal arm and then offering desirable food. Once grasped, the inability to release the grasp, to open the hand in a controlled fashion, becomes a source of frustration. The monkey has to work the food from between the closed fingers with the mouth, or with the normal hand if this is freed, and the energy of his annoyance seems to overflow, as it were, into the paretic hand, and to close it the tighter. Outright anger, on the contrary, and fright usually cause the fist to open wide, as does, also, inattention. When examined in the manner usual for proprioceptive reflex grasping (that is, by putting the finger-flexors under tension) the difficulty with letting go can sometimes be detected in tense but tractable animals, as a steadily maintained, feeble closure of the affected hand, curiously passive in feeling; but usually the finger flexion yields under even this slight pull. Reinforced by apprehension or resentment, it occasionally reaches the proportions of forced grasping, most convincingly when the animal, in struggling, chances to grab the affected foot with the affected hand and then tugs in anger, seemingly unable to let go.

Scratching is an example of a performance stereotyped in its digital component, but with a large, non-stereotyped element of aim in the postural preliminary. Pyramidal lesion virtually eliminates all scratching for months, except as tonic associated movement occurring aimlessly in conjunction with vigorous scratching by the normal side. Later, on the rare occasions when it occurs primarily and exclusively in a paretic extremity, the rhythmic digital movement is well executed, although slow

to start and ragged, whereas the postural orientation of the extremity to the site of stimulation is so defective that the scratching is as often executed in the air as at the skin. The habit of emptying the food pouch of the paretic side by rubbing it on the shoulder is another performance by axial musculature and the proximal musculature of an extremity which is eliminated. Here, neck, trunk and shoulder musculature must co-operate in a non-stereotyped fashion. Such losses prove conclusively that the selective attack of pyramidal lesion is directed on a type of usage, not on a locus—specifically on non-stereotyped usage regardless of the parts employed.

Associated movement.—In addition to the obviously purposive and more or less successful performances so far described, the side affected by pyramidal lesion displays a variety of non-purposive movements in conjunction with purposive movement elsewhere, which suggest the "associated" movements of human hemiplegia. The purposive movement may involve the normal, or the paretic side of the body, or both, or the head. The associated movements are usually tonic, but occasionally phasic. In general they are slow to develop and widespread, and both their extent and vigour are a function of the vigour of the purposive movement. Although they exhibit great variability in the details of composition, most of which must be omitted, they follow certain general patterns which may be described.

In the arm, associated movement usually mirrors the tonic or postural component of a performance by the normal arm. Thus whenever the normal arm and hand are vigorously engaged in stuffing food into the mouth, or in similar pursuits, the paretic arm is internally rotated, elevated and adducted at the shoulder, flexed and half supinated at the elbow, fingers flexed and adducted, and the wrist neutral. On the other hand, if the normal arm is strongly pronated, as is required to groom or to scratch certain parts of the body, the paretic arm also pronates, with wrist and fingers flexed. The associated movement further follows the normal in that it augments while the latter flexes, and relaxes while the latter extends. Extension, as an associated movement, is less frequent in the arm, but is seen, together with adduction at the shoulder and fanning of the digits, in conjunction with extreme torsion of head and body to the affected side. Passively turning the head has no such consequence.

In the leg, associated movement may either mirror a tonic component in the normal side, or reverse it. A flexor sequence, consisting of protraction at the hip, flexion at the knee, dorsiflexion, lateral deviation, and eversion at the ankle and extension and fanning of the toes, presents in

reverse in conjunction with strong extension and retraction of the normal leg for large righting or shoving operations in which the body and arms are also employed. It has not been observed with extension of the normal leg alone. As a mirror movement, it may accompany scratching by the normal leg, but restricted to toes and ankle, the heel being kept on the floor for support. By far the most common associated movement of the leg is an extensor sequence composed of feeble retraction and adduction with or without internal rotation at the hip, extension at the knee, dorsiflexion and eversion at the ankle, and extension and fanning of the toes. It presents symmetrically with the normal leg whenever this extends, as in shifting posture, or in thrusting or pushing. It appears in reverse when the normal leg is strongly flexed, as, for example, in scratching, or when it is brought to the mouth to have a sore attended to. It also accompanies vigorous usage of the normal arm, as in stuffing food into the mouth, and vigorous body torsion to the paretic side. Struggling also evokes it. This associated extension is responsible for the extended position which the paretic leg so often assumes, and, in the absence of placing activity, then retains.

From above the level of lesion, vigorous biting usually brings out the flexor sequence in the arm, the leg not participating; yawning, extension of the arm, and sometimes also of the leg.

Although associated movements are most conspicuous in the extremities, only the least vigorous are so restricted. When of any strength, axial musculature is also involved, most commonly in ventro-lateral flexion with the flexor sequence of the arm, and in extension during struggling. With lateral flexion of the body, the tail also deviates to the paretic side.

Phasic associated movement has been seen only in conjunction with vigorous scratching, either by the normal side or by the other paretic extremity, and only rarely. The phasic movement is preceded and accompanied by a tonic associated movement as described. The phasic movement is slow to start and halting in rhythm. The rhythms of the two sides may be approximately in phase, or completely unrelated. In the arm phasic associated scratching usually mirrors the normal side, but in the leg it appears more often when the normal side is scratching in territory properly attended to by the paretic leg. Thus the affected foot has scratched in the air when the normal hand was scratching the paretic shoulder. Also, the paretic arm often scratches in association with purposive scratching by the paretic leg, although the reverse has not been observed.

Only the two long surviving animals have shown the phasic scratching, six weeks and five months after operation, while tonic associated move-

ments are in evidence immediately after operation. Both the leg extensor sequence and the arm flexor sequence have been observed on the first day. The tonic movements, however, increase in variety and in strength with the passage of time.

To what extent the large variety of movements of the affected side in struggling and in righting are to be classed as associated, has been puzzling because, although of the same design as associated movement, they achieve in these relationships, definite usefulness.

Muscular atrophy.—Beginning insidiously a month or two after unilateral pyramidal lesion, the muscles of the paretic arm and leg bulk less than those of the normal. At first it is hard to distinguish between the palpable effects of diminished tone, and of diminishing bulk, but by the fourth or fifth month the difference between the two sides is measurable with a tape. Measurements were routinely made of the circumference of the upper arm, forearm and lower leg in their largest part, and of the thigh just above the knee, with differences which were consistent and progressive, but never large. The atrophy, or in adolescent animals, the deficient development, is at most very mild. It is generally distributed from shoulder and hip to interosseous spaces, but graver in the leg than in the arm ; and in the arm, graver in the extensors than in the flexors. Latissimus dorsi and pectoral muscles are also affected. It is unaccompanied by the slightest trace of contracture. At autopsy, the muscles of this side appear distinctly paler than the normal.

Microscopic preparations were made from muscle of the two long-surviving animals ; cut serially in cross and longitudinal section at 15 microns and stained by Bielschowsky's silver method. The rectus femoris and brachio-radialis muscles were selected as showing the gravest wasting. On comparing the normal and maximally atrophic muscle, the atrophy is scarcely appreciable. The fibres are, on the whole, slightly smaller on the affected side, and perhaps slightly paler in staining. They show, however, no disarray of striation, no increase in number of muscle nuclei, no sign of fibre destruction, no proliferation of connective tissue, or other detectable disorder. Clearly the condition is one of simple atrophy in mildest degree. The atrophy is most easily understood as atrophy of disuse, including in the concept of disuse both deficient movement and deficient tonic innervation. Whether or not vasoconstriction played a subsidiary role by restricting over months the flow of blood to the parts, cannot be evaluated. The lack of any trace of contracture attending the considerable muscular atrophy is significant as indicating that with suprasegmental motor lesions as with peripheral nerve lesions (Tower, 1939) contracture proceeds from over-activity.

Bilateral Pyramidal Lesion.

In contrast with the slight general disorder of unilateral pyramidal lesion, bilateral pyramidal lesion is deadly. Of seven monkeys so operated, six died within five days, either on the second or third day of what appeared to be medullary œdema, or on the fourth or fifth day of hypostatic pneumonia. By the fifth day, however, the one survivor had recovered her appetite, and judging from facial expression and vocalization, was in complete contact with her environment, and in possession of her senses strictly speaking, including all forms of general cutaneous, and proprioceptive sensibility below the level of lesion. From this time on until a unilateral cortical ablation was superimposed one month later, the disorder presented by this animal is taken, with some reservation, as illustrating the specific results of bilateral pyramidal lesion. As will be shown in the anatomical section, the destruction was not confined to the pyramids. Although this one adult monkey is the only one that will be described here, the observations to be presented have been confirmed in essentials, though with significant quantitative and time differences, by study over a period of two years of a monkey in which both pyramidal tracts were cut two weeks after birth.

For the extremities, bilateral pyramidal lesion duplicates the effects of unilateral lesion on tone, reflexes and usage, with a real difference only in the animal's utilization of residual activity to compensate the defect rather than an intact opposite side. It is unnecessary, therefore, to recapitulate these effects except to note that proprioceptive and visual placing reactions, and hopping, are performed noticeably better after bilateral lesion than after unilateral, and this in spite of grave damage to the medial lemniscus. This is true, likewise, of bilateral versus unilateral lesion in cats (Tower and Woolsey, unpublished work). On the contrary, because of the increased premium upon the use of the paretic extremities, bilateral lesion renders more conspicuous the disordered condition both of grasping and of releasing grasp, although the difficulties in the apprehension, manipulation and release of objects, and in climbing are exactly those described after unilateral lesion. Avoiding these, the animal feeds by taking the mouth to the food pan like a cat or dog, exhibiting in this a carefully regulated inhibition of postural tone in the arms which is noteworthy as emphasizing the lack of any quality of spasticity.

In the field of autonomic function the bilateral lesion brings out in both adult and infant an unusual liveliness of pilomotor reaction, with a suggestion of continuous slight pilo-erection, not noticeable after unilateral

lesion. This liveliness makes a late appearance, and may very well be a by-product, as it were, of the generally greater mobilization of extrapyramidal activity to compensate the defect, a condition which may also underlie the better corrective movements. However, the inability of the animal to groom herself should also, perhaps, be considered in relation to this pilomotor hyperexcitability.

Neither this monkey nor any monkey of the unilateral series developed urinary or fæcal incontinence or retention.

Bilateral pyramidal lesion makes its outstanding new contribution to the totality of the pyramidal defect in the axis of the body—as axial hypotonia. In the musculature of neck, back and thorax the bilateral lesion creates a deficit of tone which is fully as grave as the very grave hypotonia of the hip and shoulder musculature produced by unilateral lesion, and graver than the hypotonia of more distal parts. Under the influence of gravity, the head, like that of a human infant, is unstable; the body sags passively from any point of support; the abdomen bulges under the weight of the viscera; the tail droops; the intercostal spaces are sucked in with each inspiration; and the lower ribs yield to the pull of the diaphragm. Little resistance is offered to passive movement of parts including the head, and palpation of the muscles confirms their flabbiness. The abdominal musculature, too, feels softer than after unilateral lesion, but to what extent this represents loss of a splinting action by the good side, to what extent a true further loss of tone, is hard to estimate.

The hypotonia of bilateral lesion is maximal up to ten days after operation during which time the monkey lies almost entirely passive unless disturbed. In this state, and when lying quietly later, the distribution of tone is regulated largely by posture. Lying on one side, the upper extremities tend to flex; the under, to extend. Lying prone, all extend. Lying supine, the legs extend, while the arms flex or extend according as the head and trunk are ventrally flexed or the reverse. Both somnolence and emotion enhance the automatic quality of this regulation, while alert composure facilitates its abrogation in the interests of definite purpose. Tonic neck reflexes are not demonstrable in the alert animal, but the torpor of the post-operative period is attended by a proportionate increase in tone of doughy quality, with an unequivocal proprioceptive reflex grasp, and in this condition tonic neck reflexes are readily obtained.

On the tenth day spontaneous voluntary activity resumes, beginning with the attempt to right and sit up, and from then on progress is rapid. In this course the hypotonia ameliorates somewhat, but never to the degree that the head can be held completely erect on the neck, or the

trunk on the pelvis, or one extremity support the body-weight in a positive supporting reaction. This weakness must contribute to the passivity which remains an outstanding feature of bilateral pyramidal lesion.

Bilateral pyramidal lesion also makes one new contribution of defective performance in adversive activity. This shows particularly in the head which is most free to turn. A normal monkey can turn his head on his neck through somewhat more than 90° and keep it there indefinitely, and unilateral pyramidal section does not noticeably impair the ability to do this, or only very transitorily. But after bilateral section, 30° is at first about the limit of this performance, and 60° about the maximum of recovery. Maintaining the head in this position for any length of time, a minute perhaps, which is easy for a normal monkey, is not done.

Except for the new axial weakness, bilateral pyramidal lesion differs from unilateral lesion not in what is destroyed, or lost, but in what the animal does about it ; his compensation. Where a monkey with a unilateral lesion compensates by increased usage of the normal side, employing the paretic side only in symmetrically patterned activities, or in support, deprived of this possibility of compensation, the monkey with a bilateral lesion produces, slowly and laboriously tries out, and improves or rejects a series of stereotyped performances, some of which are seen only in the infancy of normal monkeys. This series probably represents the full range of possible cortical extrapyramidal motor function. Brought out deliberately, this is obviously highly volitional activity, although some of the same patterns of activity are also present in conjunction with strong emotion, in postural and righting activities, and as associated movement. The animal usually gives the situation long consideration before beginning to act, unless volition is reinforced by emotion when the consideration is curtailed. The action is always highly purposive, regardless of whether the purpose is achieved or not. It takes place in bursts of obviously great effort, followed by intervals of exhaustion, and is astonishingly fatiguing, not merely of the will, as appeared to be the case after unilateral lesion, but of the entire animal. At first even a few moments of effort so exhaust the animal that he falls on his side, eyes closed, respiration laboured, heart accelerated. Later this condition improves greatly, but even so ready fatigability is still, two years after operation, a handicap to the monkey operated in infancy. All random and minor activities such as shifting position slightly or turning the head, which keep a normal waking monkey in fairly continuous motion, are eliminated. In place of the head movements by means of which a monkey normally surveys his environment continually these animals substitute an unusual range of movement of the

eyes, which still have normal innervation, rolling the eyes upward also to compensate for the droop of the head.

Consisting in sweeping, tremulous innervation of the entire body from head to tail and digits, the first voluntary activity is no more than an exaggeration of the tonic innervation, distributed as determined by the animal's position. Incipient righting and struggling both take this form. The attempt to assume and to maintain an upright, sitting posture is the animal's earliest concerted activity after bilateral pyramidal lesion, and, as a preliminary to this, to right. Righting is at first possible only by grasping a suitable support such as the observer's hand, the bars of a cage, or the edge of the cradle. On a plane surface, with nothing to grasp, righting goes no further than rolling to one side. Two weeks later, righting becomes possible without a support to grasp. The upper extremities first flex, with lateral flexion of the head and body to that side. Then, as the under shoulder rises from the floor, the under arm is quickly flexed and retracted under the body, and, using that arm as a fulcrum, the body is flipped or levered over, and the prone animal rises to the sitting posture by extending the arms. Obviously considerable strength is needed to shift the body-weight in this righting manœuvre.

The sitting posture, first achieved by laboriously climbing hand over hand any support available until the body is dragged upright, is then maintained only by continued support from the hands and arms, at first by grasping and suspension, later, alternatively, by tonic extension against the floor. In the second week neither of these is possible. The animal cannot pull himself fully upright, the grasp yielding under the body-weight. If set upright with the arms extended to the floor, or the hands resting on a bar, the extension, or the grasp, soon yields under the weight. By the middle of the third week, however, the sitting posture is easily assumed and may be maintained for hours.

Immediately the monkey has some control of the sitting posture, he begins to attempt to stand. This is done by leaning forward on the supporting arms and extending the legs. Because the hands are placed too close to the feet, this often results in his falling forward, precipitating him into progression for a brief distance before he topples over. Later, when standing is under better control and the initiation of progression is deliberate, the extreme slowness of that process contrasts strikingly with the previous headlong course.

Controlled progression is at first cast in the diagonal pattern, the left arm leading off, and between each cycle the animal comes to a full stop, during which the legs often give way, causing him to sit down. Progression

is then a succession of individual acts of rising, stepping and collapse. The movement of each extremity is a sudden, unsustained action. The legs are thrust forward stiffly, strongly adducted, the arms thrown or shoved forward stiffly in abduction, and between these violent movements the extremities relax. The faster the sequence, the less the relaxation. Thus at an early stage the animal can run if sufficiently excited, when he cannot walk two steps without sitting. Retraction of the legs and protraction of the arms are both incomplete, more conspicuously so than after unilateral lesion. Consequently, the feet frequently step on the hands, or hands and feet group under the body, while excessive adduction of the legs causes the feet to step on one another or even to cross scissor-like. Both feet may often be seen resting on top of one or the other hand. Because of these disorders the animal is extremely unstable and often falls. After about a week of this painful progression the animal shifts to the gallop pattern. Executed slowly, this reduces to a succession of hops. The gallop has two obvious advantages: the movements of rising and of entering the first step may be executed as one; and lateral stability is much greater. Toward the end of the month, by an excessive hop, the animal can jump short distances, as from the floor into his cage, a height of 6 in. Significantly, neither the adult nor the infant with bilateral lesion developed the easy, swinging circumduction of the leg employed in progression after unilateral lesion, which has reinforced the impression that this circumduction is an acquired compensation, employing more strongly innervated and better controlled proximal and axial musculature to assist the gravely paretic appendage.

The activities so far described approximate to familiar adult patterns. Besides these the animal brings out other reactions which illustrate both the demand which is being made for the totality of possible extrapyramidal performance, and the defective character of such performance when produced. Two of these reactions are normal only to the infancy of monkeys. The one is a fear-rage reaction in which both arms are abruptly and strongly flexed, elevated and protracted, fists clenched, the head and body ventrally flexed with the head between the arms, teeth bared, legs variably flexed or extended. In the young monkey this often develops into a full-blown temper tantrum, with violent clonic movements of the entire body. The adult monkey also shakes, but not so violently. The other is a pathetic reaction accompanying desire, or mingled desire and apprehension; excited particularly by the prospect of food. One or both arms execute a circling movement of abduction and extension, adduction and flexion,

bringing the hands back squarely to the centre of the face with the fingers clawed, and with such force that the nails dig into the skin. This is similar to the reaching-grasping movement of the newborn infant whereby it clings to the mother and orients for nursing. In the adult animal this reaction could not be made to serve any purpose, and was obviously painful. During the third week, the reaction was first modified to bring the fist, clenched, back, not to the centre of the face, but to the ear. Then it was suppressed altogether, to return again temporarily, but in the opposite arm only, after ablation of Area 6 of Brodmann and of the anterior part of Area 4. A third reaction called " the jerks "—sudden, violent, extension and retraction of the legs, flexion of the arms, retraction of the head and body, mouth open and teeth bared, eyes staring, platysma contracted—appears to be the stereotyped substrate of the normal threat reaction, executed with extraordinary violence, but completely unsustained. All these emotionally biased motor activities are, like those previously described, extraordinarily fatiguing.

In a totally different category is the almost complete muscular relaxation produced by pleasurable stimulation (massage or warm bath). This relaxation, which is general, is also to be observed in normal monkeys when the object of social grooming. In this study it served to demonstrate the complete absence of rigidity, spasticity and contracture after bilateral pyramidal lesion with a thoroughness which the adult never permitted after unilateral lesion only.

Associated movements are in evidence after bilateral pyramidal lesion as after unilateral, accompanying normal usage above the level of lesion such as yawning or forcible biting, or accompanying purposive usage of other parts below. Scope and frequency are curtailed by the necessity to employ at least three of the four extremities in support when sitting or standing, but the patterns are those described after unilateral lesion. After bilateral lesion, however, the associated movements are obviously and unequivocally identical with purposive movements of the same parts to the last detail, the only difference being in the point of recognizable end. Their character as extrapyramidal activity without special qualities is thus established. They derive from one characteristic of extrapyramidal activity in general, namely its mass organization, such that any action even the most trivial tends to bring into play the entire body musculature from neck to tail and digits, and does so in proportion to the vigour of its execution.

Sensory Control

The integrity of cutaneous sensibility, both touch and prick-pain, has been easily established in every case of unilateral pyramidal lesion. On

the application of a stimulation to the blindfolded animal the normal hand reaches for and accurately localizes the site of stimulation, and equally well for both sides of the body. Further substantiation is supplied by the fact that sores and grooming are attended to equally on the two sides. For the integrity of touch alone, a crossed contact placing reaction is perhaps the most elegant evidence. After bilateral lesion, facial expression and vocalization served to demonstrate the acuity of touch and pain sense in the one long survivor who was very friendly. Unfriendly animals restrain such expression.

The condition of proprioceptive sensibility has not been similarly easy to establish. To begin with, tests for deep sensibility inevitably excite cutaneous sensibility also unless the cutaneous nerves are blocked, and this was not done. If cutaneous stimulation be minimized, the habitual reaction to passive displacement of parts is replacement. The normal side cannot act for the paretic side, yet the passivity of the paretic side is no evidence of sensory loss as such. In the presence of a motor defect, therefore, the condition of proprioceptive sensibility cannot be established in the majority of monkeys. Exceptionally, the animal which survived bilateral lesion for six weeks and became quite tame, gave evidence by facial expression of noticing fine grades of passive movement plus touch, movement of single digits only, but the touch may have been the effective stimulus.

Although examination of the living animals afforded no clue to the absence, or presence and extent of damage to the medial lemniscus, microscopic examination of the brains showed that proprioceptive sensibility must have been variously defective in four of the six monkeys thoroughly studied, and virtually intact in two. Excluding one case with deep tegmental injury as more complicated, in three cases, therefore, a partial sensory defect must have been submerged in the motor defect of pyramidal lesion, while in two others the motor defect stood alone. The fact that these five animals presented a consistent disorder, is the best evidence which can be offered that proprioceptive loss makes no significant contribution to the defect of pyramidal lesion as described.

Anatomical Examination of the Brain-Stem

Of the ten unilateral pyramidal lesions, nine overlay the trapezoid body, and one was in the interval between this and the inferior olive. Grossly, all the lesions were complete and restricted to the one side. In one case the brain protruded into the bone defect. When the lesion was long standing, the pyramid was grossly atrophied below, and in the lesion of over two years establishment, the normal pyramid and both inferior

olives had shifted to close up the trough thus created. Fig. 8 shows the ventral surface of the medulla in this case.

The bilateral lesions were more scattered, with one lesion at the mid-olivary level, and one (that in the long-surviving animal) just above the olive. All these lesions with one exception were also complete, and in this case in which the lateral third of one pyramid had been spared, the incompleteness had been recognized during life by the discrete usage of the fingers and greater tone of the opposite side. In another case the section exceeded one pyramid laterally by almost 2 mm., but this additional destruction was not correlated with any unusual condition during the brief survival.

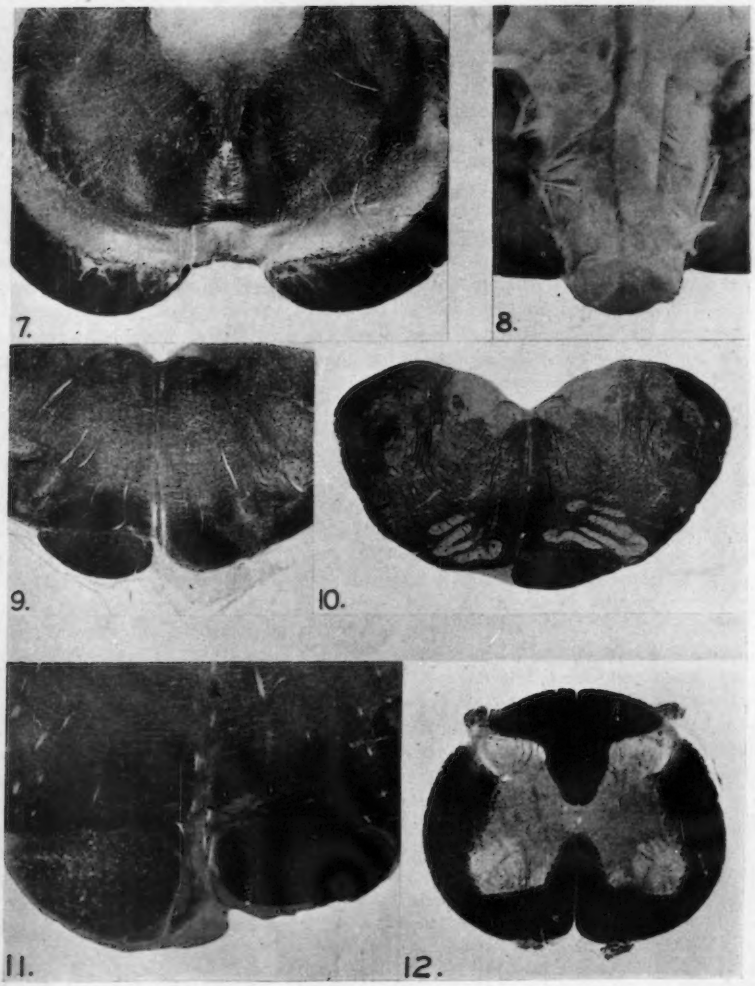
Blocks were removed for microscopic examination from the brain-stem of the six animals intensively studied, as follows: superior colliculus; mid-pons; the lesion and just below; low olivary level; C_6 or C_7; L_5 or L_6. These were prepared by Marchi or Pal-Weigert technique as recommended by the elapsed time since operation. In the two animals killed for Marchi material a block from the posterior part of the thalamus was also prepared.

Examination of the specimens taken through and just below the level of lesion confirms its completeness in every case; the pyramid is cleared of intact fibres. Figs. 9 and 11 demonstrate this for two animals. Further caudally, a few fibres make an appearance, coursing through the pyramid transversely in the line of arcuate systems as shown in fig. 10. In two of the animals, one the long survivor and one killed for Marchi material, the lesion is virtually restricted to the one pyramid, but in the other four animals, the damage goes deeper. Following are the destructions, with the available functional correlates.

M.14: Killed after two weeks; Marchi preparation. The lesion, shown in fig. 11, at the lower edge of trapezoid body, has severed the right pyramid completely and incised the superficial layer of trapezoid fibres, without invading the left pyramid or the deeper tegmentum. All the fibres of the right pyramid and about 100 fibres along the medial border of the left are destroyed, and the degeneration may be followed in both lateral and both anterior columns through C_7 and L_5 (fig. 12). At the level of lesion and below, degenerating fibres straggle up through the reticular formation, either on the same side or crossing the raphe. None enters the inferior olive. A few degenerating fibres are present in the 12th nuclei, especially the left, but otherwise all the cranial nerves and nuclei are intact. There are a very few degenerating fibres in the right medial lemniscus, traced to the lateral nucleus of thalamus, but none in the left; and heavier degeneration in both lateral lemnisci. There is no retrograde degeneration of corticospinal fibres at the mid-pontine level, or above.

Anatomically, this monkey is an example of complete and virtually uncomplicated unilateral pyramidal lesion, the involvement of the lemniscus systems, and of

PLATE II.



For descriptions see p. 90.

the remaining pyramid being, in number of fibres destroyed, negligible. Functionally, it showed the pyramidal defect as outlined, without addition, qualification or subtraction.

M.5 : Killed after two weeks ; Marchi preparation. The lesion, at the posterior border of the pons has interrupted the right pyramid completely, bruised the medial half of the left and the most caudal pons fascicles, and incised the trapezoid body to half its depth, severing medial lemniscus fibres in so doing. The deeper tegmentum is uninjured. The right 6th nerve is badly damaged, and possibly completely interrupted at its exit from the brain. Degenerating fibres may be followed in both lateral and the right anterior columns of the cord through the C_6 and L_5 levels, although the degenerating fibres in the anterior column are surprisingly few. Scattered degenerating fibres pass to the reticular formation of both sides, and degenerating fibres are present around and inside the 12th nuclei of both sides, but not inside the inferior olives. Retrograde degeneration reaches back through the medial lemniscus and internal arcuate system to the nuclei gracilis and cuneatus of both, but chiefly of the opposite side. Above the lesion degeneration is fairly heavy in the right medial lemniscus, scattered in the left ; and present in both lateral lemnisci, heavier on the right. The right corticospinal tract shows slight retrograde degeneration at the mid-pontine level, but not above.

Functionally, this monkey was more depressed postoperatively than M.14. She had a persisting internal and upward squint of the right eye, and a transitory partial paralysis of the tongue. Other than this her condition did not differ from that of M.14.

M.14: Killed after three weeks ; Marchi preparation. The lesion, at the mid-trapezoid level, has interrupted the right pyramid completely, with exact restriction laterally, and traumatized the medial half of the left pyramid without incising it. The cranial nerves are intact. From the incision a narrow region of disintegration penetrates the tegmentum in and to the right of the mid-line half-way to the floor of the 4th ventricle, extending caudally, medial to the upper pole of the inferior olive, but stopping in the cephalic direction, short of the pons. Degenerating fibres may be followed in both lateral and both anterior columns through the C_6 and L_6 levels, very few in the left anterior column. Around and inside the caudal part of the left 7th nucleus degenerating fibres are numerous, and a few are present within and around both 12th nuclei. There is extensive degeneration in both medial longitudinal fasciculi, and of fibres coursing antero-posteriorly in the right tegmentum, and into the hilus of the right olive. In the medial lemniscus and arcuate system retrograde degeneration may be traced back to the nuclei gracilis and cuneatus of both sides. Above the lesion the medial lemniscus is almost destroyed on the right side, and damaged in its medial part on the left. Both lateral lemnisci show heavy degeneration. The medial longitudinal fasciculus contains: on the right, many degenerating fibres ; on the left, a few ; and the degeneration may be followed into both 3rd nuclei. Degenerating fibres are scattered throughout the tegmentum of the pons and mid-brain of both sides but especially the right, and cross at all levels through the raphé. Retrograde degeneration has attacked the right corticospinal tract in the pons, but not above.

After operation this monkey made a rapid and uneventful recovery, the only unusual result being a voluntary paresis of the left lower face, showing most strikingly as inability to empty the left food pouch. On the third post-operative day, while the animal was in the examining chair and the head was being held,

following a violent struggle the animal became suddenly still; the eyes deviated horizontally to the left and then developed nystagmus, and without losing consciousness the animal became flaccid, with reflexes below the head practically inexcitable. This condition, complicated by nausea and vomiting, persisted for four days, and then rapidly ameliorated. On the ninth day the nystagmus was gone, and by the end of the second week the animal's condition was again, as at the outset, typical for unilateral pyramidal lesion with an additional voluntary paresis of the left lower face, and with only an ill-defined sluggishness as residue of the intercurrent episode. Presumably the onset of nystagmus and prostration signalled a vascular accident, producing the penetrating tegmental destruction.

M.2: Killed fighting eight months after operation; Weigert preparation. Protrusion of the area of lesion into the bone defect. The lesion, at the lower edge of trapezoid body, has interrupted the right pyramid completely, penetrated the trapezoid body and interrupted the superficial bundles of the right medial lemniscus. Just below the lesion there is some fibre loss in the medial part of the left pyramid, but at a low olivary level this is not perceptible. Fibre loss is conspicuous in the left lateral column of the cord through C_7 and L_5. Retrograde degeneration has thinned the fibres in the medial lemniscus and arcuate system back to the left nuclei gracilis and cuneatus. Above the lesion there is a moderate loss of fibres from both lateral lemnisci, especially the right, and grave destruction, estimated at one-third to one-half of the fibres, in the right medial lemniscus, with some suspicion of thinning in the left. The right corticospinal tract shows evidence of retrograde degeneration in the mid-pontine level but not above, and in the pons the thinning is not great.

Functionally, this monkey presented as unusual features only a transitory difficulty with the tongue and with swallowing.

M.6: Killed after thirty-two months; Weigert preparation. The lesion, shown in figs. 8 and 9, at a high trapezoid level, has severed the right pyramid completely, and virtually no more. The trapezoid body is almost untouched. Correspondingly, the medial lemniscus is also practically intact. The left pyramid shows no damage. The degeneration may be followed in the left lateral column of the cord through C_7 and L_6. There is only the slightest evidence of fibre loss in the corticospinal tract at the mid-pontine level, and none above, and even at the mid-pontine level the vast majority of the fibres are intact. Figs. 7, 9 and 10 illustrate these conditions.

Anatomically, this monkey, like M.14, appears to be an example of complete, unilateral pyramidal lesion in which the damage to other structures is negligible. This is borne out functionally by the animal's rapid and uneventful recovery, and by the absence of cranial nerve, or other accessory involvement. Together, M.6 and M.14 are taken as defining the condition of complete, uncomplicated, unilateral pyramidal lesion.

M.7: Died following a third operation, six weeks after the pyramid section; Marchi and Weigert preparations. The lesion, just above the inferior olive, has severed both pyramids completely with accurate limitation laterally. Beneath the lesion there is destruction of cells and fibres in the mid-line of the tegmentum half-way to the ventricle, but not complete as is the case in M.4. The damage is confined to the level of lesion. Degeneration may be followed in both lateral and both anterior columns of the cord through C_6 and L_6. Degenerating fibres are scattered through the tegmentum, and in the hilus of both inferior olives, but not around the 12th nuclei. Retrograde degeneration may be followed in both medial

lemnisci, back through the arcuate system to the nuclei gracilis and cuneatus. Above the lesion, half the fibres, by estimate, in each medial lemniscus are degenerated. Lateral lemnisci, trapezoid body, and medial longitudinal fasciculus are intact. There is slight evidence of retrograde degeneration in both corticospinal tracts at the mid-pontine level, but none above.

Functionally, this monkey showed the bilateral pyramidal defect as described, with a slight preference for and better usage of the left arm and leg than of the right. The grave damage to the medial lemniscus is especially noteworthy because this animal gave the best performance of proprioceptive placing and hopping obtained in paretic extremities.

Reconsidering this anatomical material, two facts are outstanding. First, damage to the cranial nerves or their nuclei excepted, the lesion may considerably transgress the limits of the medullary pyramids, without introducing variation into the symptom complex. Most significantly, damage to the medial lemniscus has ranged from nil to quite grave without this being appreciated. With unilateral lesion, slight damage to the remaining pyramid has also been without consequence except for the tongue. Although the medially lying fibres, which are the ones so damaged, are many of them corticobulbar, they are probably not all so, and the limits set on minuteness of examination by the unco-operative monkey must mask slight degrees of paresis, degrees which would, perhaps, be demonstrable in the human. Only destruction penetrating deep into the tegmentum has produced additional symptomatology within the scope of the analysis. It is noteworthy that except when the deep tegmentum is damaged, there are no degenerating fibres within the inferior olive, eliminating this source of possible confusion. Also it may be pointed out that the monkey has no external arcuate nuclei to complicate the field of operation.

Second, and basic to the argument that section of the medullary pyramids interrupts corticospinal action and that alone, is the fact that retrograde degeneration stops short almost immediately above the lesion. This means that the nerve cells giving rise to the corticospinal fibres, together with their axones down into the pons have survived amputation of their longest terminal. Whether or not they survive as giant cells is another matter which will be reported on later. It is reasonable to assume, therefore, that these cells and their prepyramidal terminals, of which the last would be the pontine collateral, are intact and functioning. If this be true, then except for the corticobulbar involvement, severing the medullary pyramids has produced the desired interruption of corticospinal function, and that alone.

Irrelevant to the present investigation, but of considerable interest in

itself, is the opposing fact that with even slight damage to the medial lemniscus retrograde degeneration reaches back through the length of the medulla, across the midline, and through the arcuate system, to the nuclei of origin. The contrast of this with the lack of retrograde degeneration in the corticospinal system suggests that, adventitious factors such as age and trauma aside, the presence of collaterals may set a limit to the extent of retrograde degeneration, perhaps by maintaining a curtailed function. The pontine collateral would thus be suspect of affording protection to the prepyramidal portion of the corticospinal neurone.

Unilateral Pyramidal Lesion in Conjunction with Bilateral Ablation of Areas 4 and 6 of Brodmann

A number of observers, working with a variety of techniques, have described the presence in the pyramidal tracts of nerve fibres arising in the post-central region. The following is an attempt to assess the functional significance of such a component. Since it is generally agreed that the prefrontal region contributes no fibres to the pyramidal tracts, this should not be difficult. By bilateral removal of Area 6 of Brodmann and of the arm and leg regions of Area 4, which was done by Dr. Marion Hines, the precentral component of fibres was eliminated. The left pyramid was then severed to eliminate the post-central component on one side only. This should bring the function of the opposite, intact post-central component, if this has independent significance, into relief. The one animal subjected to these repeated operations survived the last in excellent condition for two months, and was then killed. The disorder produced by the bilateral 4 and 6 ablation will be analysed by Dr. Hines. For this discussion, only one point needs emphasis; although such preparations are rarely if ever entirely symmetrical in their symptomatology, the asymmetry is purely quantitative.

Against the enormous hypertonus and grave paresis from the 4 and 6 ablation, the unilateral pyramidal lesion introduced on the opposite side no additional defect which could be characterized, nor did it bring into relief on the same side, any integrity of function peculiar to that side. In brief, the unilateral pyramidal lesion appeared to be completely submerged in the more comprehensive disorder produced by the bilateral cortical lesion. The examinations made in this case covered muscle tone, reflexes, general usage, and specific test performances such as placing, hopping, righting, &c. Vasomotor function was not examined.

The pyramidal lesion in this animal was located at the mid-olivary

level. Grossly, both pyramids were of good size and equal at the trapezoid level, whereas below the lesion the left was much reduced in size compared with the right. Examination of Weigert preparations showed: above the lesion at the trapezoid level, a large number of nerve fibres, fairly evenly distributed through both pyramids. Many of these are undoubtedly corticobulbar fibres, for they can be seen passing into the tegmentum at all three medullary levels examined. Below the lesion the left pyramid is characteristically cleared of fibres while the right still contains a number, though far fewer than at the trapezoid level. To what extent these remaining fibres are corticobulbar, to what extent corticospinal, cannot be determined. However, in the cord sections (C_5, C_7 and L_5 levels) it is impossible to distinguish the side opposite the pyramid section from the side opposite cortical ablation only, by a lesser fibre loss in the latter. Therefore, no great bulk of post-central corticospinal fibres can be in question.

From these results it might be surmised that post-central fibres in the pyramidal tract are of no significance functionally, even though present anatomically. This is scarcely justified. The intense muscular rigidity of 4 and 6 ablation may create a condition not unlike Parkinsonian rigidity in man, which gravely impedes even a presumably normal cortical motor mechanism. Against this rigidity, and unassisted by specific inhibitory function, a residual motor mechanism might be quite ineffectual, which nevertheless possessed, in the intact animal, definite, and even characteristic functional capacity. The experiment is, therefore, not conclusive.

Analysis of the Symptomatology of Pyramidal Lesion.

Reviewing this evidence: pyramidal lesion produces in the monkey a disorder which is conspicuous and easy to analyse against the background of residual function. The description "hypotonic paresis" covers the condition, both "flaccid" and "paralysis" being too strong terms. The concept of hypotonia must, however, be projected back of the skeletal musculature, in which the deficiency of tone is visible and palpable, to the central nervous system. Basically, it is the segmental motor mechanism which is hypotonic, producing thereby not only deficient tone in the skeletal musculature and vasomotor system, but also diminished excitability for both skeletal and vascular reflexes, and a raised threshold for all activity utilizing the segmental mechanism. Outstanding is the absence of adventitious innervation, tonic or phasic, in the form of spasticity or rigidity, or movements such as athetosis, chorea, tics or epileptiform convul-

sions. Only the associated movements suggest purposeless, but hardly excessive activity. The one instance of facial involvement likewise took this form of hypotonic paresis, almost confined to the lower face as in man.

The deficiency of pyramidal lesion is always relative to the demands of the moment, gauged by comparison with the normal side. Thus in sleep the defect is probably slight; perhaps non-existent. Lying quietly, it is apparent in tone and reflexes, skeletal and vascular, in proportion to the alertness of the animal. Sitting, it is unmistakable. But the requirement for specific performance emphasizes it in proportion to the non-stereotyped quality of the performance required. Stereotyped activity largely survives, to meet demands of this character with varying success, handicapped by high threshold and weakness. Even so, the greater part of the usage of the affected side is in conjunction with the normal side in bilaterally integrated performances in which the normal leads off.

The pyramidal lesion affects all the somatic motor mechanism below the level of lesion, and fairly equally. There is no overwhelming selection of flexor mechanism as in the cat (Tower, 1935), although characteristic lesser differences in emphasis certainly exist. A bilateral lesion is required to demonstrate this, however, because of the large ipsilateral action of the corticospinal system on neck and trunk musculature. Yet the pyramidal defect in the monkey is differentially distributed in that the tonic defect is graver in the more proximally located musculature of shoulder and hip, neck and trunk, while the paresis is graver distally—gravest in the fingers. This selectivity emphasizes the two phases of loss of pyramidal innervation to the segmental motor mechanism: a continuous or tonic deficit in effect at all times in the waking state, and a phasic or episodic deficit in conjunction with specific usage.

The tonic defect of pyramidal lesion is most conspicuous as hypotonia in the skeletal musculature, where, as in the case of the hypotonia of cerebellar lesion, it is accompanied by slow, full tendon reflexes, full because unchecked by antagonistic contraction. The analogy with the cerebellar condition goes further. The deep reflexes are unattended by adaptation reflexes, or by active rebound or after-discharge of any sort. Circumstances permitting, they may be passively pendular. Movement is sweeping, and sometimes coarsely tremulous, poorly gauged to the objective, and suggestive, in the hypermetria, of the phenomenon of past-pointing. In this connection, the very slackness of the muscles themselves must constitute a condition in which the volume of incoming sensory stimulation per unit of displacement through space is materially reduced, contributing further to delay and weaken reactions of proprioceptive origin

in the extremity responding. This would apply to reflex check contractions and reflex inhibition, and thus predispose to both pendular reflexes and hypermetria. In other circumstances, for example in bilaterally integrated performances such as progression, and in reactions such as placing and hopping, hypermetria may have a different origin, deriving from a delay of reaction on the part of a paretic extremity which necessitates an unusually long step to catch up with the normal fellow, or to bring the extremity under the body's centre of gravity.

The continuous or tonic deficit of excitation in the cord mechanism must contribute to the paresis of pyramidal lesion by establishing a high threshold for all activity utilizing the cord mechanism. On the other hand, the abolition of discrete usage of the digits and of the function which confers aim and modifiability in the course of execution upon the stereotyped extrapyramidal performances which themselves survive, seems to represent loss of a specifically timed and specifically designed corticospinal contribution to the individual act. In the case of minute usage of the digits, this may be the entire act. In contrast with the generality of the tonic loss, this phasic loss is highly selective, but selective of a type of usage, not of a locus—specifically of the non-stereotyped components in usage regardless of the part employed. For this reason only, it is most apparent in usage of the hands. Considered as movement rather than as usage, the loss is greatest of movements of the thumb of all varieties, of flexion of the index, and of extension and abduction of the fingers. Next in order, come elevation and external rotation at the shoulder, and supination of the forearm. Similar losses in the foot and leg are less conspicuous in proportion to the lesser normal frequency of discrete movement in those parts.

On a larger scale, loss of phasic action must enter into the diminished initiative which is so outstanding a result of pyramidal lesion. To be sure, the generally raised threshold for all cord activity cannot fail to depress initiative, but the overwhelming gravity of this defect can only be accounted for on the basis of a further loss of phasic action to make the total. This is certainly the case with pyramidal lesions in infant monkeys, in which the tonic defect is slight, yet the defect of initiative is very nearly as grave as in the adult. The loss of initiative applies most obviously to highly stereotyped performances such as progression which themselves survive, but reaches a maximum probably in the abolition of other similarly stereotyped activities. Viewed in this light performances may be eliminated by pyramidal lesion either because they are specific functions of the corticospinal tract in the sense that no other system is able to create the pattern,

or because they are dependent upon this tract, not for organization, but for a reinforcement that brings them to threshold. Such reinforcement could be either tonic or phasic in timing, or both. Among the digital performances eliminated by pyramidal lesion, the isolated movements of the digits must be in the first category; contact placing and contact grasping, both stereotyped, in the second.

So far, only the primary defect of pyramidal lesion has been considered. The shift of initiative to the good side which is conspicuous immediately after unilateral pyramid section, but which become progressively more so with the passage of months as the animal reorganizes his activities to employ the good side more and more exclusively, brings an additional factor to light. The initial loss must be considered primary and inescapable, but the subsequent further loss appears to be a matter of learning from the experience of ineffectiveness. The fact that the post-operative course after bilateral lesion reverses that after unilateral in that the paretic extremities are in the first case employed more and more, and in the second less and less, strengthens the opinion that a learning process influences the end-result. Judging by the puzzled and annoyed manner in which monkeys have been observed to regard the ineffectual extremity, the defect is below the level of consciousness except by recognition of the failure of performance.

In the autonomic motor field the disorder of pyramidal lesion is again most simply interpreted as a general deficiency, without phenomena of release. Indeed, this is the only interpretation which will account for all the facts without subsidiary assumptions. However, the multiplicity of factors which may enter into vasomotor function as reflected in skin temperature, beginning with four possibilities of central action: vasodilator excitation and inhibition; vasoconstrictor excitation and inhibition, enjoins caution in the analysis of this function.

By assuming a large deficit of tonic excitation in the cord dilator mechanism, and a much smaller and submerged similar tonic deficit in the constrictor mechanism, the usually lower skin temperature on the paretic side may be accounted for, yet the instances of higher skin temperature on that side may also be explained; as the result of failure of antagonistic vasoconstriction to check extreme vasodilatation. Since Kennard (1935) has demonstrated that a similar disorder produced by cortical ablation in monkeys does not operate over the posterior roots, it must operate over the anterior roots, presumably over a sympathetic outlet. Yet Bülbring and Burns (1936) failed to find any sympathetic vasodilator fibres in the monkey, although Ascroft (1937) has submitted evidence

indicating that they exist. The alternative assumption, that the usually lower skin temperature of the paretic side results from release of the cord constrictor mechanism from cortical inhibition, creates two difficulties. It permits of no obvious explanation of the rare, but by no means negligible, occurrences of higher skin temperature on the paretic side. And vasoconstrictor reflexes are not correspondingly enlivened, but, on the contrary, depressed, although much less so than dilator reflexes. Final judgment must wait on further study of the spinal and peripheral vasomotor control, specifically in the rhesus monkey.

To what extent the hypotonia in the skeletal musculature may contribute to lower skin temperature by lessened local production of heat or of vasodilating metabolites, or by lessened local axon-reflex vasodilatation, has also eluded evaluation. Since the hypotonia is minimal in the hand where the difference in skin temperature is maximal, this is probably not of much consequence. The fact that the deficit in skin temperature is greater in the hands than in the feet, whereas the deficit of tone in the skeletal musculature shows the reverse relationship, establishes the vasomotor disorder as specific—and not merely an extension of the somatic hypotonia into the visceral field, either by peripheral influences such as those mentioned, or within the central nervous system. If the mechanism at fault does, in fact, run in the sympathetic system, this segregates the central effects of pyramidal lesion on the somatic, and on the autonomic mechanisms of the extremities at least, in quite separate regions of the spinal cord.

The tonic disorder in the vasomotor mechanism is unmistakable. For or against an additional phasic disorder, there is no evidence. The slowing and enfeeblement of vasomotor reflexes, both dilator and constrictor, may equally well proceed from tonic weakness alone or involve a specific further phasic loss. Phasic cortical action might be expected in reactions such as the constriction to fear or anger, but scarcely in response to immersion of the feet in hot or cold water, that is to warming or cooling the blood stream (Gibbon and Landis, 1932; Uprus, Gaylor and Carmichael, 1936).

The occasional deficiency in the sweating function is further evidence of the basic character of the autonomic disorder as a loss of excitation, although slight, indeed.

To the question: what, if any, recovery is possible after complete pyramidal lesion in the adult monkey? a simple answer is possible. None. Compensation is, however, possible in proportion to the non-specificity of particular function to the pyramidal system. Thus, for tonic func-

tions, somatic or autonomic, in which the pyramidal tract participates with other systems, the defect of unilateral pyramidal lesion may be to some extent made up, and of bilateral lesion, to a larger extent. Defects in the initiation and execution of stereotyped performances may also be reduced with passage of time if the premium is high. On the other hand, discrete use of the musculature for aim and adjustment, or in fine usage of the digits, is irretrievably lost. Compensation in such cases must either employ the intact side, or, when this is not feasible, bend some surviving extrapyramidal performance to new ends, or recast habits radically to circumvent the loss. The nature of these measures as compensation, not recovery, is emphasized by comparison with the results of partial pyramidal lesion. Although equally enduring, these are describable only in terms of quantity of normal functions lost, not in terms of quality. And quantitative recovery is observed, up to a point.

The full range of residual, necessarily extrapyramidal activity available for compensation is brought out only with a bilateral pyramidal lesion. After a unilateral section the animal habitually employs only bilaterally organized activities such as progression, and those more or less unilateral reactions which are most indispensable such as postural activity. Following a bilateral section, however, the monkey appears to pass through a brief phase when he calls upon everything he has left. A process of selection then quickly begins to eliminate activity which is useless or the occasion of pain, and to retain useful activity. To a limited extent such activities may be gradually bent to serve new purposes.

The starting point for all activity after bilateral pyramidal lesion is a stereotyped postural pattern, the so-called "thalamic postural" or "thalamic reflex" pattern (Bieber and Fulton, 1938). When pyramidal function is abolished, this pattern at once takes control, determining the distribution of tone and early struggling and righting activities, indeed virtually the total somatic motor activity, breathing excepted, until more elaborate activities such as progression are brought into play. Yet in spite of this dominance of stereotyped posture, tonic or postural neck reflexes are not in evidence, suggesting that these, when passively produced, have an origin in common with spasticity and rigidity as phenomena of release. Nevertheless, identical patterns of innervation control the movement of the extremities in conjunction with active turning of the head, either as associated movement, or as movement posturally useful to the animal.

The associated movements of pyramidal lesion appear in a new light in this study. Presenting in spite of the hypotonia in the skeletal

musculature, in spite of the raised threshold for all activity utilizing the somatic segmental mechanism, intruding, as it were, upon an otherwise almost complete passivity, they cannot be considered as evidence of hyperactivity, or of release at the cord level. They do not, therefore, have a common origin with spasticity. Comparison of the unilateral lesion with the bilateral, both adult and infant, shows that the associated movements of the former are the prime movements of the latter, used now to definite ends, often successfully. Similar synergic movements may also be observed in quite normal monkeys in unemployed parts in conjunction with strongly innervated, purposive movement elsewhere, especially in the contralaterally homologous part. The question is: as associated movement, at what level, and how is the activity excited? The possibility can be dismissed, that pyramidal lesion at the medullary level releases the brain-stem motor mechanism from a restraint solely effective against associated movement. The associated movements are most simply understood as proceeding from an intrinsic bilaterality and mass organization of extrapyramidal activity, thrown into relief against the general passivity of the paretic parts. Certainly the circumstances evoking associated movement are such as to call for vigorous extrapyramidal action; normally, with vigorous usage in which there is a large postural component; after unilateral pyramidal lesion, again only with vigorous usage when the good side is endeavouring to do the work of both; and after bilateral pyramidal lesion, when extrapyramidal action is the only action possible. From the unimpeachable evidence of bilateral pyramidal lesion, the associated movements are extrapyramidal. Viewed in this light, as unmasking extrapyramidal action, associated movements, presenting normally or abnormally, offer a measure and a picture of the extrapyramidal substrate of total motor activity.

Granting the probability that pyramidal and extrapyramidal activity normally co-operate in any cortically initiated activity of any strength and complexity, discrete usage of the digits probably not even excepted, the question might be asked: what is associated movement, what primary? Usefulness does not seem an adequate criterion. Much of the tonic associated movement of the paretic parts may be useful as synergic postural fixation, as similar activity accompanying strongly innervated normal action obviously is. Only the phasic associated movement can be dismissed as wholly useless, perhaps to be considered as simple overflow after the example of respiratory hippus in the pupil.

Pyramidal Lesion in Man.

For man, on the contrary, the syndrome of pyramidal lesion has long been summarized in the phrase "spastic paralysis." The classic "pyramidal" signs have included, besides loss of voluntary movement and diminished or absent superficial reflexes, exaggerated deep reflexes with clonus, the sign of Babinski, and a host of other signs of less weight. However, clinical evidence incompatible with this concept has slowly accumulated. Thus Marinesco (1903) studied two young adults from whom Jonnesco had removed small pieces of the cortical hand area for epilepsy, and reached the opinion that neither exaggerated tendon reflexes, nor contracture, nor associated movements are immediate phenomena of pyramidal lesion; that these appear when movement of an extrapyramidal type returns; that flaccid paralysis is the sign *par excellence* of pyramidal injury. Dejerine's (1914) consideration of hemiplegia, which he defined simply as "un syndrome constitué par un perte plus ou moins complete de la motilité volontaire dans une moieteé du corps," described the initially flaccid character, which is common experience, but before passing on to the usual spastic second stage, stated unequivocally that occasionally the hemiplegia might remain flaccid. Before this, as the result of comparative study of cortical and capsular lesions in man, Bergmark (1910) had concluded that the spastic phenomena, exaggerated tendon reflexes and contracture, and the sign of Babinski, are not produced necessarily, nor even typically by cortical lesion, whereas capsular lesion does produce them. In 1932 this conclusion received experimental verification and further elaboration in the work of Fulton and Kellar and of Fulton and Kennard on monkeys and chimpanzees.

In 1919, Walshe had reasoned, "From clinical and experimental sources come several indications, as yet imperfectly understood, that a pure cortical lesion of the pyramidal system often does not produce spasticity as an accompaniment of the loss of power. They suggest the possibility that in the cerebral lesion underlying, for example, a typical spastic residual hemiplegia, analysis may ultimately reveal a second component. That is, that in addition to a negative lesion of the corticospinal path, interruption of another descending path may be concerned in the production of spasticity. Such a path need not necessarily be cerebrospinal." So far as the evidence then stood, however, both these systems might be contained within the corticospinal tract, one system motor, the other inhibitory to the cord. Hines' (1936, 1937) demonstration that the cortical area whose destruction results in spasticity is a part of Brodmann's Area 4, is not incompatible with this view.

Because of the widespread origin of the corticospinal tract in the cortex, and because of the fact that all this area gives rise also to numbers of extrapyramidal systems, evidence derived from cortical lesion or ablation is able to indicate, but not to establish, the symptomatology of pyramidal lesion. Theoretically, only subcortical destruction, and that only in the narrow reach of the medullary pyramids, can establish this. For man there appears to be on record no case with anatomical verification of destruction restricted to one or both medullary pyramids. Környey (1936) has described a case, diagnosed as embolism of the left arteria spinalis anterior, in which the condition of the affected arm approximated closely to that of the monkey after unilateral pyramidal lesion. The arm hung dependent under the influence of gravity; the muscles were hypotonic, and the grave atrophy (in reality, failure to develop) was unattended by contracture. However, the deep reflexes were described as "erheblich gesteigert." Additionally, position sense was disturbed over the affected upper extremity, and the opposite half of the tongue was paralysed and atrophied. At the time of writing this patient was still alive 26 years after the onset.

Two cases reported by Markowski in 1891 and one by Lewandowsky in 1905, and perhaps another by Nothnagel in 1879, may be taken, cautiously, to indicate that destruction of the corticospinal tract in its course through the pons in man may produce flaccid paralysis. More to the point, however, are two cases published by Davison (1937) as "Syndrome of the Anterior Spinal Artery of the Medulla Oblongata." The first of these had a flaccid left hemiparesis, with impairment of deep sensibility and two-point discrimination, and with involvement of the right 6th, 7th and 12th cranial nerves. The second had a spastic right hemiplegia, with some involvement of the left side also, with slight ataxia on the left side, and impaired deep and cutaneous sensibility on the right. Both cases had a positive Babinski. In both these cases, which were thoroughly studied anatomically, the lesion had destroyed more than the medullary pyramids, in both cases attacking the medial lemniscus. Yet of the two, the flaccid hemiplegia had been produced by a fairly restricted lesion, whereas the spastic paralysis was the result of widespread destruction, reaching up through the tegmentum to destroy the thalamo-olivary tract and part of the vestibular nuclei, and laterally into the corpus restiforme, with all the possibilities thus introduced. There were lesions elsewhere in this brain also.

A case reported by Goldscheider (1891) makes an interesting comparison with this last case of Davison's. The lesion in Goldscheider's

case likewise destroyed all of one pyramid, the right, and part of the other, also part of the right olive, and extended up through the right tegmentum to the floor of the 4th ventricle. It differs from Davison's case chiefly in sparing the lateral tegmentum, and thus approximates to the lesion in M.4. This individual's paralysis was described as "schlaf."

Medullary pyramidal lesions without impairment of deep sensibility are rare. Mauss (1908) has reported a case (No. 1) of hemiparesis without hypertonus or spasm but with increased deep reflexes, with integrity of touch and proprioceptive sense but dissociated loss of pain on face and body. The diagnosis was embolism of the left posterior inferior cerebellar artery. There was no autopsy. Vastly more significant is the case currently being studied by Hausman (1939), and still surviving, of pure flaccid hemiplegia unaccompanied by sensory defect. In this case the term "flail-like" is applied to the hypotonic condition of the extremities, the abdominal reflex is absent, the deep reflexes are again described as increased, and the Babinski sign is present. With a history of gradual development over seven years, this case as it now stands almost certainly represents the closest approximation to unilateral pyramidal lesion yet recorded for man, but anatomical verification of this surmise is not yet possible.

The citation of cases may be concluded with Case 3 reported by Schlesinger in 1897. A variety of destructions, ranging from softening of the right supramarginal gyrus to syringomyelia of the thoracic cord, renders this case equivocal, but among these was a lesion destroying the left pyramid at a low olivary level and the adjacent portions of the inferior olive and medial lemniscus. The last was not reflected in any recognized loss of proprioceptive sensibility. The paralysis of the right arm was flaccid at the shoulder, but accompanied by a slight flexor contracture of elbow and hand. The point of interest in this case is the observation that the paretic extremity was colder and more livid than its fellow. This is the sole mention made of vasomotor condition throughout this human material.

Imperfect as the evidence is, the cases cited build up a syndrome of pyramidal lesion in man corresponding with that in the monkey in the prime features of hypotonia and paresis. The description of the deep reflexes in man as "increased" or "gesteigert" is an apparent discrepancy, which might be removed by differential examination of their space- and time-dimensions. In the monkey the deep reflexes are often large in space but slow in time for reasons analysed. None of the studies of man except the last makes note of vasomotor condition, and none describes

in detail what is actually lost in the paralysis, and what, if any, motor performance survives.

Exceptionally, Davison's second case records the condition of the corticospinal tracts above the lesion. The peduncles appeared normal, and in the pons the pyramidal tracts were not demyelinated almost two years after total interruption of the right medullary pyramid, and nine months after probable partial destruction of the left. In man, therefore, as in the monkey, the cells of origin and prepyramidal course of the corticospinal fibres may survive, and therefore perhaps function, after destruction of their spinal processes. Since adventitious factors such as age, nature of the destructive process, and general physical condition may very well influence the viability of the prepyramidal portion of the cell, and hence the effective destruction, the condition of the prepyramidal portion of the corticospinal neurone should be determined anatomically in every case. This may be one cause for the variability of the symptomatology from so-called pyramidal lesions in man, even perhaps from lesions of the medullary pyramids.

The usual hemiplegic condition in man permits of more complete comparison with the result of pyramidal lesion in the monkey, simply because it has been more thoroughly studied. Setting aside phenomena of release—spasticity, tonic neck reflexes, and contracture—the similarities are striking. Habitual postures are similar in the monkey and in man, even though in the monkey these are not set in contracture. The so-called Wernicke-Mann predilection in hemiplegic paralysis is similar to, though not identical with, the predilection of paralysis in the monkey. Outstanding in both man and monkey is the elimination of non-stereotyped components from usage of all sorts, with preservation of stereotyped components in a weakened condition. The associated movements of hemiplegic man, and of the monkey with pyramidal lesion, are remarkably similar. The quantitatively much graver total motor loss in man may be either a species difference, deriving from the relatively greater cortical dominance in man, or the result of additional destruction in hemiplegia, of extrapyramidal motor systems. Probably the two sum. The variability of vasomotor condition from case to case of hemiplegia in man may likewise derive from varying components of pyramidal and extrapyramidal destruction. With respect to muscular atrophy in hemiplegia, Brissaud (1880, p. 79) long ago described it as appearing first in the shoulder and thenar eminence, an opinion expressed again lately by Winkelman and Silverstein (1934)—that is, in muscles outstandingly inactivated by pyramidal lesion in the monkey. Finally, although the

monkey has no pathological sign of Babinski under any circumstance, precluding comparison with man on this point, drawing upon unfinished work, the sign of Babinski does accompany pyramidal lesion in the chimpanzee, as well as hemiplegia in man.

With hemiplegia in man, as with unilateral pyramidal lesion in the monkey, the disorder is largely appendicular. As yet the evidence is insufficient to show whether or not uncrossed pyramidal innervation has in man the large share in axial innervation which it has in the monkey, although Beevor (1909) has uncovered a suggestive ipsilateral effect. More troublesome is the evidence from hemiplegic man purporting to show bilateral pyramidal innervation of the extremities. The evidence of bilateral weakness offered by Dignat (1883) and by Pitres (1889) will have to be reconsidered in the light of the pronounced bilateral operation of the extrapyramidal systems which were in part also destroyed. A similar critique will also have to be applied to compensation in hemiplegia, to distinguish pyramidal from extrapyramidal action by its form. Since, however, there seems to be on record (Zenner, 1898) one case of hemiplegia with lesion and symptomatology confined to the same side, accounted for anatomically, by failure of the pyramids to decussate, the occurrence in man of ipsilateral appendicular control must be granted, although its prevalence may still be disputed.

Digesting all this material, the final inquiry may now be undertaken: What are the reliable signs of pyramidal lesion? In man and the chimpanzee, the sign of Babinski, but this serves only for the foot. Since the hypotonia of pyramidal lesion is so easily obscured by the spasticity or rigidity of auxiliary extrapyramidal involvement, therewith also altering the character of the deep reflexes, tone and the deep reflexes are unreliable. Vasomotor condition also seems subject to confusion, probably on similar grounds. Only the superficial reflexes appear equally defective with any level of corticospinal lesion, but these are scarcely weighty evidence. With an intact spinal and peripheral neuromuscular mechanism, impairment or loss of the ability to execute isolated movements, most conspicuously of the digits, but equally, if proper tests be applied, of more proximal musculature, appears to be the only general applicable and reliable sign of pyramidal lesion, or strictly speaking, of loss of pyramidal function. Conversely, the ability to execute isolated movements, whether of the digits or of more proximal parts, is indubitable evidence of function of the pyramidal tracts. Thus the one unique function of the pyramidal tracts—their minute control of the skeletal musculature—appears in default as the one reliable sign of pyramidal lesion,

affording, moreover, a quantitative measure of the status of pyramidal function which may be topographically applied to all parts.

Summary of the Functions of the Pyramidal Tract.

Reinterpreting the results of pyramidal lesion, the functions of the pyramidal tract are characteristically organized both in space and in time. The spatial organization derives from a relatively stable topographical relationship between loci in the cortical field of origin of the tract and loci in the motor mechanism of the spinal cord. The fineness of this topographical organization underlies the unique feature of corticospinal function: the ability to bring into action any portion of the skeletal musculature, and in all combinations. This detailed control of the skeletal musculature enables the discrete usage of the musculature, especially of the digits, and the modulation of extrapyramidal activity, which are outstanding pyramidal functions. Furthermore, by increasing the excitation in specific portions of the segmental mechanism, it may enable fragments of the stereotyped patterns of extrapyramidal activity to be brought to threshold as part reactions, detached from the frame which usually gives them usefulness. The pyramidal tract operates in a crossed relationship on the extremities, but bilaterally on the axial musculature other than abdominal.

The functions of the pyramidal tract are not, however, covered by description, no matter how detailed, of results of stimulation in its field of origin because the organization in time is not in this manner brought out. In time, the pyramidal tract operates in two phases. On the one hand is a continuous, or tonic action in effect at all times in the waking state. On the other hand is a specifically timed increase of discharge, or phasic action, which is evoked in relation to particular situations. The tonic function contributes to the excitatory state throughout the spinal cord, supporting muscle tone, keeping thresholds low, facilitating, reinforcing, steadying and moderating whatever tonic or phasic activity may be set in train at segmental or suprasegmental levels. The delivery of this excitation is not to all parts equally, but is influenced by original preponderance, and by postural and other immediate factors. Its volume is a function of the temper of the individual and of extraneous factors of great variety, reaching its lowest level short of sleep when the animal verges on sleep either from exhaustion or from boredom.

The phasic, or episodic function initiates movement or speeds initiation. It enters into all somatic motor activity of any complexity, to confer on the stereotyped extrapyramidal performances: adjustability in space,

modifiability in the course of execution, and all the modulations of pattern which make for aim, accuracy, economy, lability and finish. More than this in the primate, this function enables the discrete usage of the musculature, and especially of the digits, which is characteristic of the order.

Together, the tonic function provides for smooth, continuous, efficient action while the phasic function contributes, outstandingly, precision and lability to total performance. In the realm of somatic motor function both of these are unquestionably motor or excitor functions. Of inhibitory function as such there is no evidence.

On the vascular system, the corticospinal system likewise exercises a continuous influence in the waking state which supports dilator tone and facilitates, reinforces and moderates reflex action. Whether this influence is excitatory of dilatation, or inhibitory of constriction is uncertain. Also whether or not there is a further phasic action has not been determined.

Function of the pyramidal tract is thus co-extensive in time at least with the waking state, and determined in intensity by both general and specific demands of that condition. It is distributed to the entire somatic motor mechanism of the body, and to parts of the autonomic mechanism, the survey of the autonomic relationship being as yet incomplete. It is organized in complexity to match virtually the full range of activity, from simple tonic functions wherein it merely assists, to complicated performances which are primarily its responsibility. Although traditionally, the pyramidal system has been considered "the voluntary motor pathway," this is too sweeping. An impressive capacity for voluntary movement survives pyramid section, especially if the lesion be bilateral, forcing the issue. Conversely, some activities eliminated by pyramidal lesion, for example the contact placing reactions, must be considered, if not involuntary, at least highly automatic. By virtue of its tonic action on the spinal cord, pyramidal function must assist all somatic motor activity, if not, indeed, all motor activity of the waking animal, at whatever level initiated even the spinal reflex level without regard for the voluntary or automatic quality of particular acts. As the agent of lability, however, the pyramidal tract makes a unique contribution to total performance. Together, the all-pervading, and the discriminating qualities of corticospinal action afford the cerebral cortex that influence in virtually all realms of final motor action, and that minuteness of control which determine its effectiveness as an agent of choice. In this service of choice the pyramidal tract is unquestionably the outstanding, though not the exclusive voluntary motor pathway.

REFERENCES.

ARING, C. D. (1935), *Amer, J. Physiol.*, **113,** 3.

ASCROFT, P. B. (1937), *Brit. Jour. Surg.*, **27,** 787.

BEEVOR, C. E. (1909), *Brit. Med. Jour.*, **1,** 881.

BERGMARK, G. (1910), *Brain*, **32,** 342.

BIEBER, I., and FULTON, J. F. (1938), *Arch. Neurol. Psychiat.*, **39,** 433.

BRISSAUD, E. (1880), Recherches anatomo-pathologiques et physiologiques sur la contracture permanente des hémiplégiques. Thèse de Paris.

BÜLBRING, E., and BURN, J. H. (1936), *Jour. Physiol.*, **88,** 341.

DAVISON, C. (1937), *Arch. Neurol. Psychiat.*, **37,** 91.

DEJERINE, J. (1914), Semiologie des Affections du Système Nerveux. Paris.

DIGNAT, P. (1883), *Progrès Médical*, **11,** 761.

FLECHSIG, P. (1876), "Die Leitungsbahnen im Gehirn und Rückenmark des Menschen auf Grund entwicklungsgeschichtlicher Untersuchungen."

FULTON, J. F., and KELLAR, A. D. (1932), "The sign of Babinski. A Study of the Evolution of Cortical Dominance in Primates." Baltimore.

——and KENNARD, M. A. (1932), *Proc. Assoc. for Research in Nerv. & Ment. Disease*, **13,** 158.

GIBBON, J. H., and LANDIS, E. M. (1932), *J. Clin. Inv.*, **11,** 1019.

GOLDSCHEIDER (1891), *Charité-Annalen*, **16,** 162.

HAUSMAN, L. (1939), Trans. Amer. Neurol. Assoc.; Sixty-fifth Annual Meeting, p. 217.

HINES, M. (1936), *Amer. J. Physiol.*, **116,** 76.

——(1937), *Bull. Johns Hopkins Hosp.*, **60,** 313.

KENNARD, M. A. (1935), *Arch. Neurol. Psychiat.*, **33,** 537.

KÖRNYEY, ST. (1936), "Schädigung der Pyramidenbahn im Hirnstam." Bumke & Foerster, *Handb. der Neurol.*, **5,** 446.

LEWANDOWSKY, M. (1905), *Monatschr. f. Psych. u. Neurol.*, **17,** 495.

MARINESCO, G. (1903), *La Semaine Médicale*, **23,** 325.

MARKOWSKI, S. (1891), *Arch. f. Psych. u. Nervenkrank.*, **23,** 367.

MAUSS, T. (1908), *Dtsch. Ztsch. f. Nervenheilk.*, **34,** 398.

NOTHNAGEL, H. (1879), "Topische Diagnostik der Gehirnkrankheiten." P. 99. Berlin.

PITRES, A. (1884), *Arch. d. Physiol.*, **3,** 142.

ROTHMANN, M. (1902), *Ztsch. f. Klin. Med.*, **44,** 183.

——(1907), *Arch. f. Anat. u. Physiol.*, Phys. Abth., 217.

SCHLESINGER, H. (1897), *Ztsch. f. Klin. Med.*, **32,** Suppl., 50.

SCHÜLLER, A. (1906), *Wien. Klin. Wochensch.*, **19,** 57.

TOWER, S. S. (1935), *Brain*, **58,** 238.

——(1936), *Ibid.*, **59,** 408.

——(1939), *Physiol. Rev.*, **19,** 1.

TÜRCK, L. (1851), Sitzber. d. K. Akad. d. Wissensch., Wien, Math., Natur Classe, **6,** 288.

UPRUS, V., GAYLOR, J. B., and CARMICHAEL, E. A. (1936), *Clin. Science*, **2,** 301.

WALSHE, F. M. R. (1919), *Brain*, **42,** 1.

WINKELMAN, N. W., and SILVERSTEIN, A. (1934), *Proc. Assoc. Research in Nerv. & Ment. Disease*, **13,** 485.

ZENNER, P. (1898), *Neurol. Centralbl.*, **17,** 202.

PLATE I (p. 53).

Photographs taken two weeks after section of the right medullary pyramid, M.14. Lesion shown in fig. 11.

FIG. 3.—Showing the drooping left shoulder, and flabby arm and fingers. The incision may be seen in the ventral mid-line of the neck.

FIG. 4.—Simultaneous failure of visual, contact and proprioceptive placing reactions in the paretic left arm.

FIGS. 5 and 6.—Simultaneous failure of visual and contact placing reactions in the paretic left leg. A normal positive supporting reaction in the right leg.

FIG. 6.—The "lift" reaction; failure of the paretic leg to extend in order to maintain contact with the supporting surface.

PLATE II (p. 69).

Untouched photomicrographs. (Figs. 7—10), Weigert series from M.6, surviving operation thirty-two months. (Figs. 11 and 12), Marchi series from M.14, surviving operation two weeks.

FIG. 7.—Mid-brain: showing integrity of nerve fibres in the basis pedunculi, and in the lemniscus systems of both sides.

FIG. 8.—Ventral view of medulla, pia not removed: Showing complete atrophy of the right pyramid with integrity of the left. Both the right inferior olive and the left pyramid have shifted to fill in the defect. The emerging 12th nerve rootlets are conspicuous on the left.

FIG. 9.—Lower border of the lesion, low trapezoid level: showing total elimination of the right pyramid with integrity of the left. The right medial lemniscus and the caudal strands of the trapezoid body have dropped down to fill the defect. The nerve-free tissue ventral to these is scar tissue, replacing the destroyed pyramid and extending into the dural and bone defects. (This picture is reversed left for right by comparison with the rest of the plate.)

FIG. 10.—Mid-olivary level: Showing elimination of the right pyramid, with a very few transversely coursing arcuate fibres in the supporting tissue remaining. The right inferior olive, medial lemnisci and left pyramid have all shifted somewhat to close the defect.

FIG. 11.—Lower border of the lesion; low trapezoid level: showing complete destruction of the right pyramid with integrity of the left except for a very few scattered degenerating nerve fibres in its medial part. Degeneration also of the superficial fibres of the trapezoid body.

FIG. 12.—Spinal cord, L.5: showing degeneration in the left lateral column.

THE ANGIOARCHITECTURE OF THE GLIOMATA.

BY JAMES HARDMAN.

Much has been written on the histological differentiation of the primary tumours of the nervous system and a general agreement attained as to their various classifications and subdivisions. Although unanimity as to nomenclature has not been reached, the varieties are sufficiently well recognized to be identifiable by the neuro-pathologist. The authors who have done pioneer work in the differentiation of the gliomata have desscribed the blood-vessels of the tumours so far as these seemed to be important. But attention was focused chiefly on the relationship of the cell to the vessel, rather than on any marked eccentricity of vessel type, still less has the general plan of the blood supply been studied.

It was the writer's object to study the plan of the angioarchitecture of the gliomata so that there might be a correlation of the histological findings with the angiographic picture obtained *in vivo;* that is, this study is concerned not only with the cellular structure of the vessel walls, but with the general plan of the circulation in the gliomata which alone can explain why the vessels are of different forms in different parts of the tumour. The fortunate use of Pickworth's method has allowed of a study rather wider than the original intention, embracing both benign and malignant gliomata.

Previous Work on Angioarchitecture of Tumours.

It was but natural that attention should be focused on the cellular elements of the gliomata rather than on the vessels which they contain and this the more because their differentiation and classification presented such difficult and debatable questions. Comparatively little work on vessel types has been done, probably because there was no method which was capable of contributing information on a big enough scale. And yet these vessels tell a story could it but be read.

Tooth (1912) was one of the first to observe peculiarities in the vessels of the malignant gliomata; he illustrated what he called "glomerular multiplication" of vessels on the border of an area of necrosis. He contributed several other points, e.g. on the endothelial proliferation which

might be so great that it obstructed the vessels, on organized thrombi, and on "glia proliferation" around the small vessels (the last was probably an adventitial reaction). Tooth also noted the multiplication of small vessels at the edges of area of necrosis in the less malignant gliomata, a finding which the writer has confirmed. Tooth's work was done before the days of modern classification of gliomata; his observations are none the less worthy of respect.

Bailey and Cushing (1926) also mentioned the occurrence of proliferation of the endothelium and of hyaline degeneration of the walls, leading to occlusion of their lumen and to necrosis of adjacent areas in malignant tumours. Carmichael (1928) was the first to point out that the glioblastoma multiforme is one of the most vascular types of tumour. Whilst in the brain substance wide of the tumour he found the vascular formation normal, at the edge of the tumour there was very great excess of capillary vessels, closely packed together, their walls composed of a single layer of endothelial cells with no fibrous sheath. Within the tumour proper the vessels were less numerous but distinctly larger, and surrounded by a definite fibrous coat. The fibrous tissue was not limited to the immediate vicinity of the vessels but spread out into the tissue in a radiating manner, though never to such a degree as to allow the tumour to be called fibrous. Derry (1932) made a special study of the histology of the vascular changes in the vessel walls of glioblastoma multiforme. He found that the changes were not specific as they occurred in lesser degree in other conditions, including other tumours. The distribution, type and degree of the hyperplasia of the vascular elements varied greatly; large areas of tumour contained only normal vessels. Elsberg and Hare (1932) cut long radial strips of brain and tumour, stained them in the usual manner and enumerated the number of vessels per field. These were expressed on paper according to their relative position in the tumour. It was concluded that "Upon gross and microscopic examination of post-mortem material, the difference between the number of blood-vessels in the central and peripheral parts of the tumour and the adjacent brain tissue are striking. In the astrocytomas and medulloblastomas the largest number of vessels occur in the central parts of the growth, there is no increase in the number of arteries in the adjacent white matter. In the glioblastoma multiforme, the peripheral areas of the neoplasm contain the largest number of arteries and the vessels in the adjacent brain tissue are more numerous than in normal white matter, or in the brain which is adjacent to the margins of the astrocytomas and medulloblastomas." Elvidge, Penfield and Cone (1937) reviewed fifty-six tumours of the glioblastoma multiforme

type. After discussing the tumours generally they turned to the blood-vessels and confirmed the foregoing findings. They stressed the proliferation of the endothelial lining of the vessel towards the lumen, which might be an important factor in the production of obstruction of the circulation. Occasional vessels were seen to be completely filled with these endothelial cells again, canalization of closed vessels could take place. When the endothelial cells appeared to bud in an outward direction, new vessels were formed, so that a glomeruloid mass of capillaries or a great mass of endothelial cells without vessel formation resulted. The similarity between this description and the original of Tooth will at once be recognized.

All these descriptions emphasize the changes undergone by the walls of the vessels without giving any clear idea of the blood supply as a whole and its response to neoplastic formation.

Available Methods of Study.

In the studies alluded to the vessels of cerebral tumours were studied after staining by ordinary histological technique, or by Perdrau's mode of impregnation of the connective tissue of the blood-vessels. By these methods an indication may be obtained of the distribution, size and number of the vessels and of the changes in the vessel walls. But it is difficult to recognize the nature of individual small vessels, or to form a general conception of the pattern of the vascular plexus and the relations of its component vessels, even when thick sections are used.

Many investigators, Beevor (1909), Fay (1925), Pfeifer (1928), Shellshear (1929 and 1930) and Wislockie (1936) used injection methods to reach an understanding of the ultimate distribution of the blood-vessels of the normal brain. The present writer in his first series of experiments used similar methods and injected a suspension of barium sulphate in hot gelatin into the internal carotid and vertebral arteries of those who died of intracranial tumour. The brain was then removed, fixed in formalin, and sectioned into slices one centimetre in thickness. Each slice was radiographed. Further sections were prepared and stained by ordinary histological technique. This method was used on eight normal and eleven tumour cases and was finally proved to be unsatisfactory because only the large vessels could be distinguished, and except in sections 250 microns thick the capillaries could not be seen. The injections might, therefore, appear to be superficially satisfactory and yet the capillary bed was frequently incompletely shown. When injections are made under pressure, extravasations occur in the tumour especially in the zone between active and necrotic tissue and these spoiled the specimens. Nevertheless, some interesting observations were made on this material, e.g. that the tumour vessels were much more fully injected than the capillaries of the surrounding white matter, whether close by or at a distance, and that there was a tendency for the injection mass to pass through the tumour into the veins. The tumour was thus demonstrated to be clearly an area of low resistance. Appreciating the deficiencies of the injection technique it was discontinued in favour of a microchemical process

evolved by Pickworth (1932), a suggestion made by Dr. J. G. Greenfield and now gratefully acknowledged. Sections 250 microns thickness are treated with benzedrine, sodium nitroprusside and hydrogen peroxide. Hæmoglobin interacts with the reagents to form a black precipitate. The method is similar to that described by Lepehene (1919), who used an almost identical technique for the staining of blood-corpuscles present in tissue cut in thin histological sections. All blood-vessels that contain hæmoglobin are stained by this procedure, it is sometimes possible to trace the course taken by the blood from the arterial to the venous side of the capillary circulation. By using a uniform technique with all sections of the same thickness by photography and enlargement to the same degree, a series of pictures is obtained that can be utilized for comparison of one part with another, and of case with case. Variations in the vascular bed throughout a tumour can be readily discerned and the findings controlled by observations upon tissues adjacent and remote from the tumour. It is an advantage that thrombosed blood-vessels and blood extravasations can be recognized. Negative results must be accepted with reserve, because the delineation of blood-vessels by this method is dependent upon their containing blood-corpuscles. It is realized that many factors influence the distribution of the blood in the brains of patients who die from cerebral tumour, and that the allocation of the blood may be different after death. Such alterations, however, can have little influence on the channels in which the blood lies, in the sense that they could not make it appear that vessels existed where there were actually none. On the other hand the absence of vessels in Pickworth-stained material is not absolute evidence that none is present and a cross-check with other stains is needed to verify their non-existence. Increase in the volume of the intracranial contents by tumour growth, increased tissue fluids, or cerebrospinal fluid, can only occur with a corresponding decrease in the intracranial blood content. Experience has shown that in tumour cases the cerebral capillaries (as distinct from those in the tumour) do not stain as well as in normal brain no doubt because of relative cerebral anæmia in the terminal phases of life. But in practice the method has proved highly satisfactory, even on glioma material, if a sufficient number of blocks were cut from different parts of the tumour and its environs.

Material.

This investigation is based upon the examination of material obtained from twenty-three autopsies and two operation cases. The material is classified into two large groups, the malignant and the relatively benign gliomata, but it is realized that there are transitions of vascular patterns from one to the other; some tumours exhibit features of both. Using Hortega's classification the malignant group comprises six glioblastoma-heteromorphe and eight glioblast-astroblastoma. A single example of Schwannoid oligodendroglioma is included among the malignant group because a single example showed the same vascular response. No pure oligodendroglioma has been examined as yet. Among the benign gliomata are ten cases, which include the astroblast-astrocytomata and the astrocytomata. It is recognized that the size and rapidity of growth are not the sole factors influencing the duration of the patient's life, although the terms malignant and relatively benign are used in this sense. The malignant gliomata include all tumours more malignant than the astroblastoma; this rare tumour never shows necrosis and presumably would show the same features as the benign tumours.

The Anatomy of the Normal Vascular Pattern.

A knowledge of the normal is essential before attempting to assess pathological changes in the blood-vessels of the brain. Textbooks of anatomy dismiss the subject after describing two types of vessels, the long and short perforating end-arteries. Radiographs of slices of brain with the arteries injected with suspension of barium, show these two types distinctly. The short perforating vessels appear to be confined to the grey matter whilst the long perforating vessels, fewer in number, run a straight or spiral course towards the centre of the hemisphere: a uniform calibre appears to be maintained until the vessels disappear. Their path appears uninfluenced by the tracts in the white matter. The anterior and

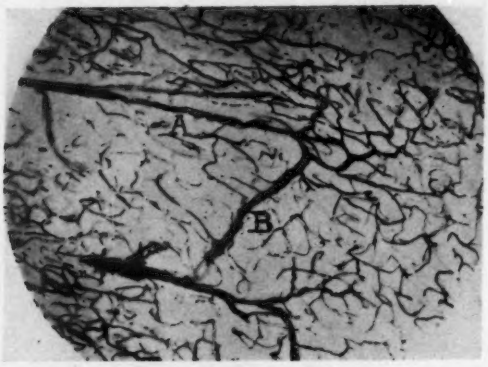


Fig. 1.—The normal capillary network seen in the cortex. A represents an arteriole, while B is the venule draining the capillaries of A. Pickworth staining. (×60.)

posterior perforating arteries arise from the circle of Willis and middle cerebral vessels, run a long course and supply the basal ganglia, though some of them terminate in the choroid plexus. Fay (1925) pointed out that injection of a main branch of the circle of Willis filled other vessels of the same or even the opposite hemisphere. Pfeifer (1928) showed illustrations that reveal a rich capillary anastomosis of all vessels supplying the brain. Sections of brain stained by the present writer with the Pickworth technique confirm this finding and also the observations just mentioned. The short perforating vessels seen in fig. 1 break up immediately into a rich capillary plexus with a very fine mesh. From the deepest parts (not shown) communications occur with the capillaries of the white matter. The long perforating vessels seen in fig. 2 run on parallel courses,

linked together by short, fine, interlacing capillaries and forming a distinctive pattern. The picture differs, of course, depending on whether the section is made parallel with or transverse to the long arteries. Vessels with a wider lumen (fig. 1B) than the arterioles (fig. 1A) are found, their radicles arising from the capillary bed of the white and grey matter; these are the venules of the cerebral veins. The arrangement of the capillary network varies a little from one part of the brain to another. In grey matter, cortical and basal, the capillaries form a characteristic fine mesh, whilst in the white matter the vascular plexus is more open. Uniformity of pattern is maintained. The manner in which this funda-

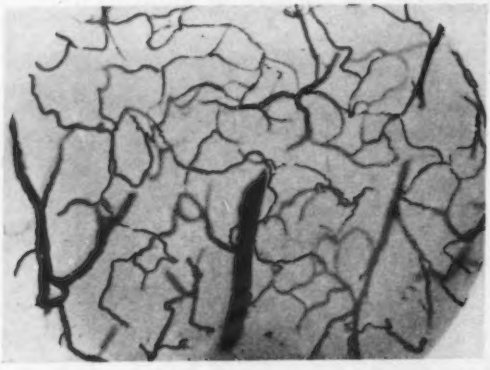


FIG. 2.—Normal capillary network in the white matter. Pickworth staining. (×60.)

mental pattern comes to be altered, amplified and distorted by tumour growth will shortly be seen.

THE VASCULAR BED OF THE MALIGNANT GLIOMATA AS SEEN BY THE BARIUM INJECTION METHOD.

Though the barium gelatin method of investigation was abandoned after many failures to delineate the capillaries of the brain, two examples of malignant gliomata so treated revealed that the suspension of barium sulphate had passed through the vascular bed of the tumour into the veins draining it. It was one of these that gave the first insight into the general arrangement of the angioarchitecture of these tumours, and indicated why it was impossible to inject the capillary bed of the surrounding brain. A radiograph of a section of one of these allows analysis of the vessels

into four zones (fig. 3). From without inwards these were (A) normal brain which showed only arterioles injected, this gradually merged into (B) the region of active tumour which contained vessels much larger and more numerous than those seen in the surrounding brain. In the deepest portions of this layer were large sinusoids (C). In marked contrast is the necrotic centre of the tumour (D) which was free from injected barium. The vessel (E) is the tortuous and grossly displaced anterior cerebral artery, while the vessel (F) represents one of the anterior cerebral veins filled with

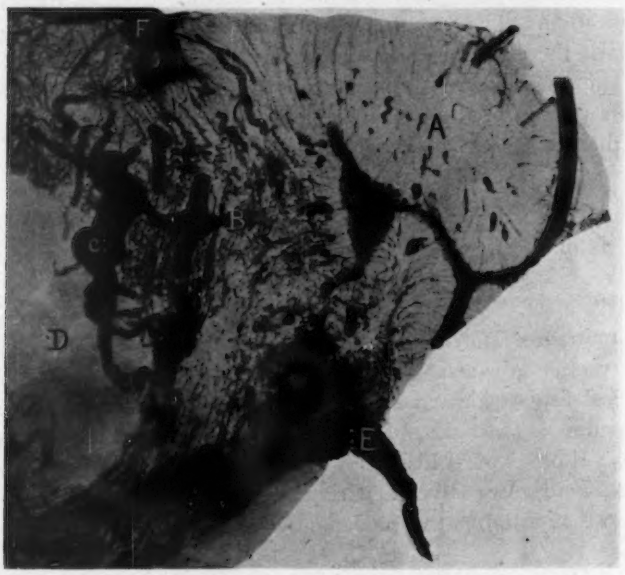


FIG. 3.—Radiograph of a portion of brain from the region of a glioblastoma multiforme. A, B, C, D indicate the different zones of the vascular pattern. E is the anterior cerebral artery. F is one of the anterior cerebral veins.

barium gelatin. Microscopical examination of thick sections revealed that surrounding capillaries had been poorly injected with barium. About the time that this specimen was obtained, Tönnis (1937) had just postulated the existence of arterio-venous anastomosis in glioblastoma multiforme. Olivecrona (personal communication) had observed that the veins draining malignant gliomata often contain bright red blood. It was thought that this tumour presented an excellent opportunity for demonstrating the existence of arterio-venous anastomoses, but a careful examination proved negative. The injection mass passed through into the veins because of

the very rich bed of dilated capillaries and sinusoids in the living part of the glioma and not because of direct anastomosis between arteries and veins. Indeed the suspension passes through the tumour so readily that it is impossible to inject the capillaries of the rest of the brain satisfactorily. These findings suggest that a similar state exists during life. Attempted removal of these tumours is often accompanied by rapid loss of a large quantity of blood and exploratory puncture can sometimes be followed by a sharp flow of red arterial blood. This type of bleeding is usually easily arrested, which would not be like the bleeding from an arterio-venous communication. Though there is no true anatomical arterio-venous anastomosis the effect must be similar because the capillaries are dilated and the sinusoids so large. It is possible that this short-circuiting of blood through a portion of the altered vascular network may affect the circulation of the brain as a whole.

The Angioarchitecture of the Malignant Gliomata.

The complete angioarchitecture of the malignant tumours could only be fully recorded by a description and illustration of each case, for no two are exactly alike. All that can conveniently be done is to describe the more important features common to them all. The changes undergone by the vessels are best illustrated by strips, which consist of serial histological fields taken on one axis from the periphery to the necrotic centre of the tumour. In order to make the pictures sufficiently comprehensive, a short clinical history will be given as well as the pathological findings. Four cases have been chosen, each a little different from the others, so that variables can be demonstrated.

Case 1.—History and clinical signs. Mrs. S., aged 54, was admitted to the Salford Royal Hospital, October 21, 1937. She had suffered from occipital headaches for one year, and after June 1937, showed signs of mental deterioration. During the preceding nine weeks vomiting occurred frequently and on one occasion she temporarily lost the use of the left side of the body. When admitted to hospital the patient was found to be drowsy, disorientated, would not co-operate and was unable to give her history. Examination revealed bilateral papillœdema and left pyramidal signs. There was incontinence. A diagnosis of right frontal tumour was made. This was confirmed at autopsy November 7.

Histological picture.—Histologically the tumour proved to be a glioblastoma heteromorph. The invasive edge was ill-defined. The active portion of the tumour was narrow and consisted of glioblasts, astroblasts, giant cells, compound granular corpuscles, and many cells with mitotic figures. The vessels were numerous and larger in calibre than normal capillaries. In those parts adjoining the necrotic centre the tumour had an area of semi-necrosis, pyknotic nuclei were heaped up

around the vessels. These vessels were larger than any others in the tumour, they had thick adventitial walls in the meshes of which were smaller vessels. Some of these larger vessels showed ante-mortem thrombosis and polymorphonuclear cells adhered to their lining endothelium (fig. 13). At one point the vessels had an angiomatous appearance. At no part was endothelial proliferation a feature. The central necrotic area consisted of cell debris with pyknotic nuclei. The vessels of this zone were large and had thin walls, their lumen contained either degenerated red cells or pink-staining material.

Angioarchitecture.—Pickworth stained material (fig. 4, Plate III), showed that the surrounding white matter had a comparatively normal capillary network (A). Separating it from the tumour there was a large vein that had been divided longitudinally (B). This represented one of the pathways of venous return from the vascular bed of the tumour. The active tumour contained large sinusoids that showed marked tortuosity and diversity of calibre. One large sinusoid (C) in the very centre of this zone showed complex looping. In the outer part of this region

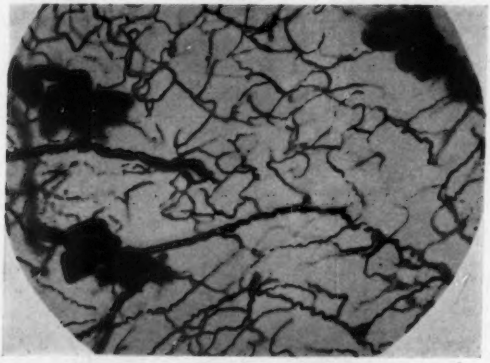


FIG. 5.—A zone taken just outside the area infiltrated by tumour. Note the tortuosity of the capillaries and the even more pronounced looping in the course of the three venules. Pickworth staining. (×45.)

an occasional capillary could be distinguished. The central necrotic area (D) was stained by points of prussian blue, the result of old blood extravasion. A faint greenish punctate deposit represented the ghostly outline of the thrombosed sinusoids.

At the point where active tumour approached the cortex of the hemisphere, the capillary network was dilated and tortuous. Three of the venules showed a similar change to the sinusoid with the complex looping (fig. 5).

Case 2.—History and clinical signs. J. R., aged 44, was admitted to the Neurosurgical Service of the Manchester Royal Infirmary. Two months previously he had complained of tiredness and a nasty taste in his mouth. Four days before admission he experienced headache, vomiting and drowsiness. His condition deteriorated and he was admitted to hospital unconscious. On examination he was found to have an early papillœdema and left pyramidal signs. On October 12, 1937,

angiograms of the right side showed the presence of convoluted vessels in the depths of the frontal lobe just behind the fronto-parietal suture in a circular area which measured 4 by 4 cm. This was thought to indicate a glioblastoma multiforme. The patient died twenty-four hours later. At autopsy a spherical tumour measuring 4 by 6 by 6 cm. was found deeply placed in the right hemisphere, lying external to the anterior horn of the lateral ventricle. Its centre was cystic and contained 3 c.c. of yellowish fluid.

Histological picture.—Histological examination proved that the tumour was a glioblastoma heteromorph. The active region of the tumour contained glioblasts, astroblasts, multi-nucleated giant cells, and astrocytes. In the peripheral part of the tumour there was a row of capillaries which had undergone localized dilatation and whose wall showed some endothelial change (fig. 9). Pickworth stained material (fig. 10) demonstrated that this reaction had been fairly extensive. Capillaries could be traced to the region of the small aneurysmal dilatations, and venules could be seen leaving them. In the deeper parts of the active tumour pseudo-pallisading was a pronounced feature (fig. 12). The more central the section the more numerous and larger the vessels became. At first, narrow columns of tumour cells separated the vessels. Immediately adjoining the cyst, large vessels with thick walls and a broad sheet of fibrous tissue replaced the tumour cells.

Angioarchitecture.—Examination of sections stained by the Pickworth method (fig. 6) showed that the surrounding capillary plexus (A) was poorly delineated. In the peripheral part of the tumour (B) small tortuous sinusoids interspersed with capillaries were to be seen. In the deeper zones the sinusoids were more numerous, and there were no capillaries. This part corresponded with the area showing pseudo-pallisading and intervascular necrosis (C). At the edge of the cyst (D) the sinusoids were closely packed into a complex mass.

Case 3.—History and clinical signs. J. B., aged 55, was admitted to the Neurosurgical Service of the Manchester Royal Infirmary, January 14, 1938. Four months before being admitted to hospital the patient had frequent severe headaches; he had lost consciousness for one or two seconds on three occasions. In December 1937 he became much worse, his memory was impaired, vomiting was frequent, and he was incontinent and unco-operative. He had bilateral papillœdema and slight left pyramidal signs. The pupils varied, at times they dilated, at others contracted to the size of pin-points. Death occurred January 25. At autopsy only the brain was examined. The right temporal lobe was voluminous and replaced by a necrotic tumour that measured 7·5 by 3 by 6·5 cm. The outer aspect of the globus pallidus was grossly involved. The cut surface of the tumour showed a yellowish granular surface, surrounded by a greyish translucent zone 3 to 4 mm. thick. Some parts of the tumour were pseudo-encapsulated. Blood was found in the cisterna pontis and there were small hæmorrhages in the formatio-reticularis of the mid-brain. There was a pronounced tentorial pressure cone.

Histological picture.—Sections stained by Hortega's variants showed the tumour was a malignant glioblast-astroblastoma. The cellular parts consisted of glioblasts, astroblasts and astrocytes. There were no giant cells. Mitosis was frequently distinguished. The vessels were numerous and were larger than capillaries, their walls were made up of one or two layers of endothelial cells. Sections stained by Hortega's method for connective tissue demonstrated that even the small capillaries had some connective tissue in their walls. Nearer the centre, the vessels became a

PLATE III.

FIG. 4.

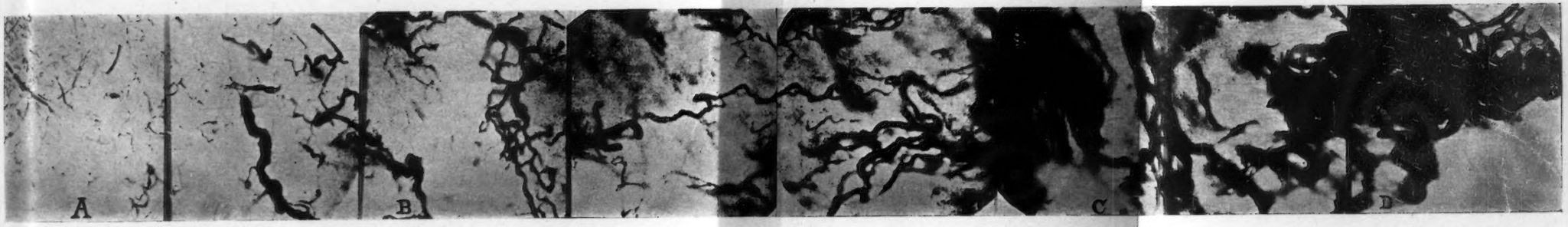


FIG. 6.

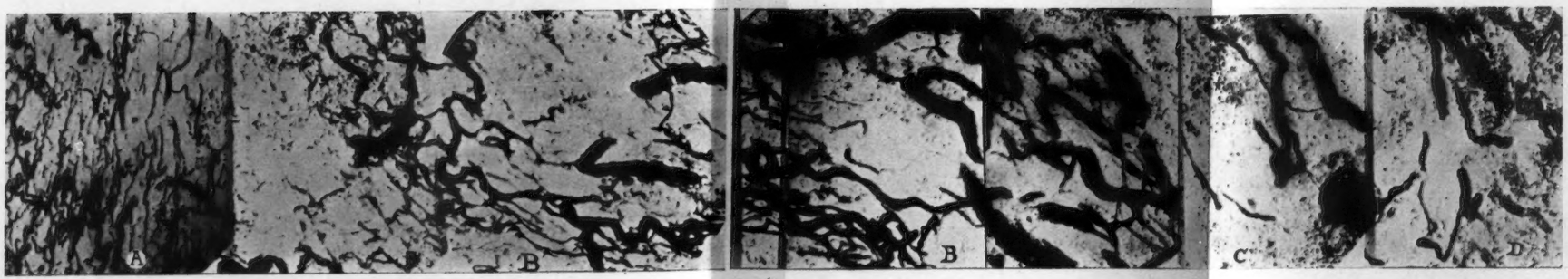


FIG. 7.

FIG. 8.

For descriptions see p. 118.

little larger and the amount of connective tissue had increased. Sections taken from the anterior pole of the tumour showed a line of capillaries in which endothelial cells had undergone some proliferation (fig. 9). Pseudo-palisading could be seen in the deeper parts of the active tumour (fig. 12). The transition from active to necrotic tumour was fairly readily defined. The vessels at this point were sinusoidal but not numerous, their walls showed some adventitial thickening but it was not excessive. The necrotic centre had the usual appearance of cell debris and pyknotic fragmented nuclei, with extravasation of blood corpuscles. There were many fair sized vessels whose lumen contained cell debris, and whose walls showed some reduplication of the adventitia.

Angioarchitecture.—Sections stained by the Pickworth method (fig. 7) demonstrated that the capillary network of the surrounding brain was represented by interrupted black dots (*see* fig. 6A). At the point where the tumour approached the cortex (A) the capillaries had a wider calibre than normal and were tortuous, several of the venules showed marked looping. In the active cellular portion (B) there were many small sinusoids and dilated capillaries. One or two parts of this network showed evidence of blood extravasation along the course of the vessels. The semi-necrotic portion of the tumour (C) in which there was pseudo-palisading (fig. 12) contained large sinusoids which were widely spaced, they tended to run a comparatively straight course. The necrotic zone (D) stained green owing to old blood extravasation. There were many large thrombosed vessels.

Case 4.—History and clinical signs. W. W., aged 49, was admitted to the Neurosurgical Service of the Manchester Royal Infirmary, January 9, 1938. On September 23, 1937, he experienced a foul smell for the first and only time. Twelve hours later the patient had headache, was light-headed and weak down the left side of the body. After this, the headaches were frequent. On examination, cerebration was a little delayed, though memory was good. Sight was impaired. There was papillœdema and pronounced left pyramidal signs. Tactile sensation of the left side was slightly impaired and there was astereognosis and complete loss of joint sense of the left upper limb. Ventriculography confirmed the diagnosis of a right parietal tumour. On January 10 a right osteo-plastic flap was raised and exploratory puncture was carried out through the intact dura and a sub-cortical tumour found and deemed inoperable. The incision was closed without opening the dura. The patient suddenly became comatose and died January 25. At autopsy a large right parietal tumour was disclosed which measured 6 by 5·5 by 4·5 cm. The cut surface was variegated in colour, having areas of hæmorrhage and necrosis interspersed with firmer bands of grey tissue. The margin of the growth was ill-defined, at some parts there was pseudo-encapsulation. The whole of the right hemisphere was œdematous.

Histological picture.—Sections stained by Hortega's varient showed that this was a glioblast-astroblastoma. It was made up mainly of astroblasts, glioblasts and occasional astrocytes. Mitosis was not recognized. This portion of living tumour contained sinusoids with thickened walls. Bounding the necrotic zone at one point there was a sheet of fibrous tissue that contained many small vessels, while adjoining it was a part where tumour cells and large sinusoids occurred. The necrotic centre consisted of cell debris and numerous vessels with mild adventitial changes in their walls and whose lumen was filled with debris. In the peripheral parts of the necrotic zone there were numerous polymorphonuclear cells and compound granular corpuscles.

Angioarchitecture.—Pickworth stained material (fig. 8) revealed that at the periphery of the tumour invasion (A) the capillary network was broken and represented by short black lines. In the region corresponding to living tumour (B) there were sinusoids with a fair proportion of capillaries. In sections of this thickness the vessels failed to form a continuous network. At another part of the tumour the vessels showed reduplication. Surrounding the central necrotic area (C) there was a well defined zone in which there were numerous small sinusoids and irregularly dilated capillaries, which formed a very rich plexus of vessels. The central necrotic area was stained green by extravasated blood.

Comment on the Angioarchitecture of the Gliomata.

In the malignant cases, of which examples have been given, as seen with the Pickworth technique, the vascular pattern was fairly constant, except for differences in degree. By the barium injection method four zones were distinguished and were made the basis of the foregoing analysis.

Zone "A."—The capillaries of the surrounding white matter were poorly stained: they were often represented by an interrupted stream of black dots (fig. 6A). The vessels of the surrounding white matter might fail to stain at all; in other cases the capillary plexus had been compressed laterally. Sometimes where the tumour approached the overlying cortex, the capillaries were a little dilated and tortuous, while the venules showed complex looping (fig. 5). This later phenomenon was described by Cerletti (1911) and was recently illustrated again by Campbell, Alexander and Putman (1938). The writer has repeatedly observed at operation that at the edge of the malignant gliomata the pial vessels show exactly the same characteristics.

Zone "B."—At the invasive edge of the tumour the vessels stained more constantly because they contained more blood. The orderly normal uniform network became chaotic, the capillaries were interrupted and irregularly dilated, and an occasional sinusoid was visible (figs. 6B and 7B). In the more malignant tumours it was found that capillaries were scarce and sinusoids common (fig. 4). The number of sinusoids per unit of area varied in different tumours and in different parts of the same tumour; in some they were massed together, in others widely separated. Many of the sinusoids exhibited marked diversity of calibre and in some cases the complex looped arrangement of Cerletti (fig. 4c), in others they were comparatively straight (fig. 7B). It would seem that, the more malignant the tumour, the fewer the capillaries, for only the less malignant varieties of glioblast-astroblastoma contained capillaries throughout the whole thickness of the tumour tissue (fig. 8).

Zone "C."—As a rule the sinusoids were largest but fewest at the edge of the necrosis. In fig. 6 they were shown to become larger and more

numerous in the deeper portions of the tumour, while in fig. 4 the sinusoids were fewest in the peripheral part of the active tumour. The more benign varieties of glioblast-astroblastoma showed a mass of dilated capillaries forming a rich plexus bordering the necrotic centre.

Zone "D."—Every malignant tumour had a necrotic centre in which there were thrombosed sinusoids and blood extravasation (fig. 4D). Case 2 had a central cyst but this was the result of a colliquative necrosis, a not unusual finding.

The vessel walls in the zones.—It should be instructive to compare these findings with the histological structure of the vessel wall in the various zones, especially with a view to making comparison of endothelial

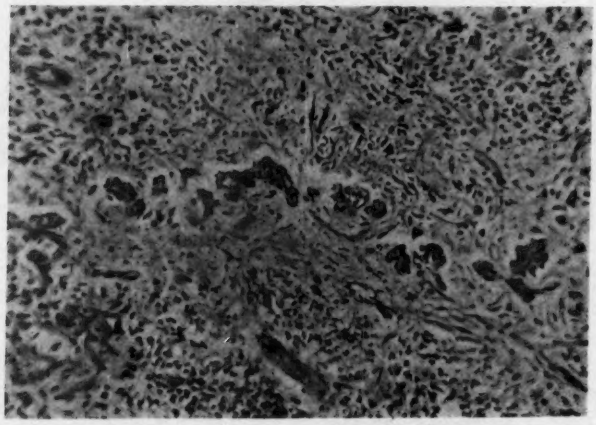


FIG. 9.—Endothelial changes seen in the capillaries of the active peripheral part of the tumour. (Hæmatoxylin eosin ×150.)

and adventitial changes. It will be recalled that the capillaries of the brain are made up of a single layer of endothelial cells together with occasional adventitial cells. The endothelial cells are able to proliferate, either by budding outwards as ill formed new capillaries, or as a solid mass of endothelial cells, further they may cause a reduplication of the capillary wall, or bud inwards, thus filling the lumen of the larger sinusoid. The adventitial cells possess the capacity for producing connective tissue fibrils, this latter propensity being particularly well seen in the malignant gliomata.

Zone "A."—The walls of the capillaries contained in the surrounding white matter did not reveal any change worthy of comment.

Zone "B."—In the outer part of this region endothelial change was encountered on four occasions. It has been referred to in the past by Tooth, Derry, Elvidge, Penfield and Cone as "glomeruloid," and in this study was found only in the superficial parts of the tumour where capillaries still existed. The endothelial change affected adjoining capillary loops so that it appeared to occur in linear formation. At this point their lumen had in some cases undergone localized dilatations but in others building up of endothelial cells narrowed the lumen. On the side of the tufts directed towards the centre of the tumour there was always a space,

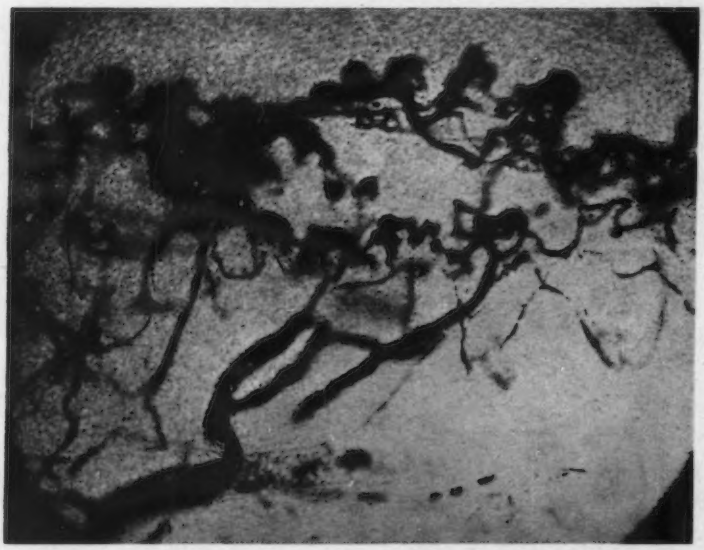


FIG. 10.—Aneurysmal-like dilatations on capillary loops from the adjoining portion of tumour shown in fig. 9. Note the venules which drain the area.

which was far too constant to be an artefact (*see* fig. 9). Corresponding sections stained by Pickworth technique (fig. 10) revealed additional features: the endothelial reaction occurred at the site of aneurysm like dilatation of the capillaries, while venules drained the area. These findings strongly suggest that this reaction represents an adaptation of the capillary wall to facilitate cellular interchange and removal of the katabolites of actively proliferating tumours cells.

Adventitial proliferation was seen in almost every tumour of this group, but the degree varied from case to case. In the peripheral regions

of the tumour even the capillaries showed some connective tissue thickening of their walls This observation would indicate that the vessels of this class of tumour are produced by a modification of existing capillaries rather than by proliferation of new vessels.

Zone "C."—In this zone adventitial thickening of the walls of the large sinusoids was always a prominent feature. In several of the cases a sheet of fibroblasts enclosed the necrotic area and in the more benign cases surrounded a rich plexus of closely woven dilated capillaries (fig. 8c). In this region the type of endothelial change which has been most stressed was observed on one occasion, it consisted of endothelial proliferation towards the centre of the lumen of the larger sinusoids. It has been thought that this change is an important factor in the production of necrosis, but owing to the rarity of its occurrence the writer thinks that its importance is, in that sense, doubtful.

Zone "D."—In the necrotic centre only an occasional vessel was seen to possess a patent lumen. The majority were filled with a hyalinized pink staining material or cell debris. Many of the vessels showed an adventitial proliferation which had persisted from the time before the area became necrotic. Some of the less malignant glioblast-astroblastomata showed the necrotic area almost entirely replaced by fibrous tissue.

The vessels of the malignant gliomata are produced by dilatation of pre-existing vessels together with the laying down of connective tissue. The deeper and presumably older part of the tumour has the fewest but largest vessels with the greatest amount of connective tissue in their walls. Endothelial proliferation does occur, but it does not take the form of new capillary formation in the malignant tumours. When present it occurs in the capillaries of the superficial and more active parts of the tumour. In the more benign examples of glioblast-astroblastoma new capillaries are produced in the fibrous tissue bordering on the necrotic centre. It will be shown later when considering the benign gliomata that capillary formation is a prominent feature ; this does not imply that the vessels are of recent origin but that they have been developed specially to meet the needs of tumour cells whose division occurs comparatively slowly and whose vessels have presumably been in existence for some time.

The Relationship of Vessel Type to Necrosis.

In the malignant gliomata the greatest degree of cellular activity and differentiation is seen in the outer zone, in contrast with the centre where there is always fibrosis, hyaline change and sometimes degenerative cyst

formation. At the periphery of the neoplastic permeation of the surrounding tissues, a normal or slightly dilated capillary plexus appears to suffice the requirements of growth. In the centre degeneration is linked with vascular disorganization and indeed includes the vessels as well as the tumour cells. Since this central necrosis is so constant, and, no doubt so closely related to the general vessel plan, it is important to consider the factors involved in bringing it about. Two have been suggested. Tooth (1912), Bailey and Cushing (1926), Elvidge, Penfield and Cone (1937) believed that proliferation of the endothelium and hyaline degeneration in the walls of the vessels led to their occlusion, with consecutive necrosis of the central area. In the present series internal proliferation of endothelium was observed only once, so this is unlikely to be an important factor. Derry (1932) suggested the second possibility, that necrosis was caused as much by local toxic effects as by decreased blood supply. At the moment it is felt that there is insufficient evidence to give an opinion upon this second theory; the influence of this factor must wait on new knowledge.

It is reasonable to suppose that a capillary plexus supplies the tissues with materials correct in all proportions for normal life and provides a vehicle for the dissemination of normal cell products. These conditions may not be satisfied in tumour tissue, where blood may not serve adequately the wants of perverted cell function, or bear away fully the products of its activity. It has been shown that a malignant tumour does not possess a uniform vascular plexus throughout its substance, there is a gradual transition from normal capillaries at the periphery of a tumour to the wide sinusoidal channels of its innermost preserved layers and then disorganization of all tissues in the central zone. The malignant cells possess the power of rapid proliferation so that the life of the individual cell is short. This power of division continues so long as the cells are in a favourable medium, as may be obtained by transference from time to time from one tissue culture to another or by repeated implantation into a new host. This multiplication of cells does not encourage stability, the scene of activity is constantly shifting. The individual cells are rapidly displaced by their descendants and the fight for existence is waged not only with the adult cells of the host, but amongst themselves, those cells more favourably placed as regards blood supply continue dividing, but the more centrally situated cells find themselves with diminishing facilities for cellular interchange, proliferation becomes slower and slower and the cells become more closely packed together, until eventually necrosis occurs. Tumour cells are considered to be embryonic in type but they do

not possess the tendency to survive and progress in an orderly way to other cell forms which is one of the great attributes of normal embryonic tissue. This power is linked with the orderly formation of a blood supply, vessel formation keeping pace with cellular division and differentiation. In a malignant tumour survival with differentiation is the cause of different cell patterns which may be found in various microscopical fields in a tumour. The death of the patient or the necrosis of the tumour naturally cuts this process short. But the constant occurrence of necrosis in malignant gliomata appears to be nothing else than a page in a biological

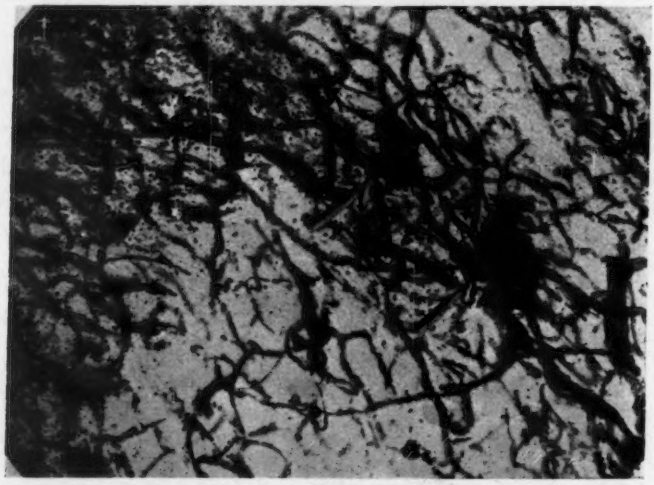


FIG. 11.—The vascular bed seen in that area of the tumour containing small foci of necrosis. Note the numerous dilated vessels. The arrows indicate punctate hæmorrhages as also the stippling.

story and cannot be as accidental as is suggested by the theory of deprivation of blood supply by endothelial proliferation. The fact that tumour cells can continue to proliferate when care is taken to supply a suitable medium suggests to the writer that *in vivo* the peculiarities of the blood supply, which they themselves induce, is a strong contributary factor in their demise.

The majority of the malignant gliomata possess a characteristic vascular pattern gradation, this represents the end result of a series of changes which have been provoked by tumour invasion. To form a conception of the way this has arisen it is necessary to study an earlier phase, as seen in the one case which had not the characteristic picture and which

represents the earliest changes so far encountered; they occurred in a specimen of a glioblast-astroblastoma obtained from a patient aged nine who died eight weeks after the onset of the illness. The tumour was reddish grey in colour and on microscopical examination showed numerous small foci of necrosis, small hæmorrhages and dilated capillaries. In Pickworth stained material the capillary mesh was about normal in size for white matter but it was interrupted and the capillaries a little dilated. In the area of focal necrosis the capillaries were more dilated and numerous (fig. 11). From this observation, as well as from the others already described, it is clear that neoplastic permeation must bring about distor-

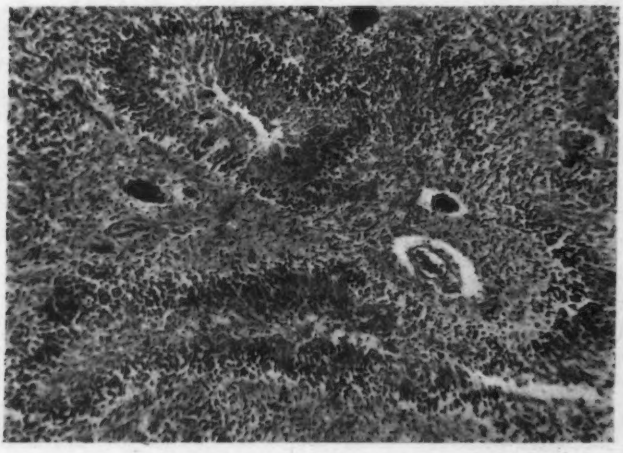


FIG. 12.—Areas of necrosis surrounded by heaped up pyknotic nuclei. The sinusoids are seen lying between these. (Hæmatoxylin eosin ×80.)

tion of the normal lattice of blood-vessels. By cellular proliferation some of the vessels are compressed and others dilated by obstruction. Capillary channels rupture giving rise to minute blood extravasations and small scattered foci of necrosis in the tissue they supplied; many vessels thrombose and disappear whilst vessels in their immediate vicinity dilate, possibly in response to the breakdown products of tissue protein (fig. 11). This phenomenon may be analogous to the transitory phase of inflammatory-like dilatation of vessels observed by McDonald and Woodhouse (1938) in the early stages around sarcoma transplants in the thigh muscles of mice.

If an area in the capillary bed becomes necrotic the volume of blood

normally destined for the involved area must of necessity be added to that coursing through the surrounding patent channels; so that this in itself may be a stimulus to dilatation. Thoma (1893), Clark (1918) and Hughes (1935, 1936 and 1937) have shown that the size of a vessel in developing tissue is dependent upon the rate of blood flowing through it, the rate of increase in size being greater for veins than arteries. The large vessels seen in malignant gliomata are abnormal channels developed from the dilated capillaries of the white matter. Earlier in this paper it was suggested from observation on injection material that these vessels offer less resistance than the surrounding capillary network to the cerebral

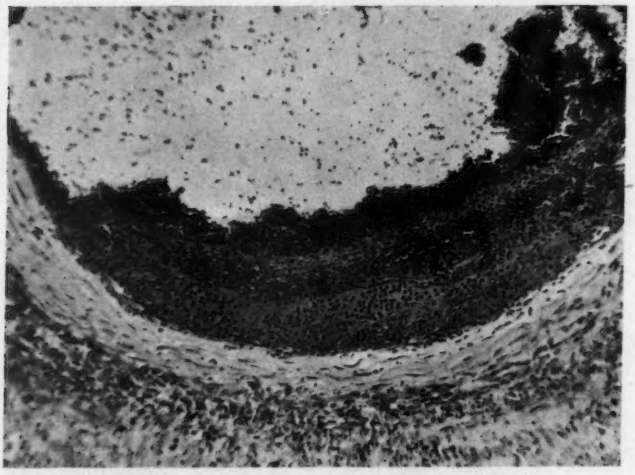


FIG. 13.—Cross section of a large deeply placed sinusoid showing ante-mortem thrombosis with gradual narrowing of the lumen. (Hæmatoxylin eosin ×80.)

circulation. A vicious circle is established by the dilated channels tending to convey more and more arterial blood and becoming more dilated. They acquire an adventitial wall which increases in thickness. In seven cases of this series the area bordering on the necrosis shows the sinusoids surrounded by living tumour cells, but between these there are small foci of necrosis around which are the heaped-up pyknotic nuclei of degenerated cells, giving the characteristic appearance of pseudo-palisading (fig. 12). If the necrosis is occurring more rapidly the pyknotic nuclei form a mantle around the sinusoids. Pickworth stains (fig. 7c) demonstrated that the sinusoids are widely separated, suggesting that the

more distant cells are deprived of a means of interchange with the blood-stream.

The further invasion of the surrounding brain by tumour is accompanied by the formation of more peripherally placed sinusoids and blood is short circuited from the deeper parts of the tumour, so that the central area of necrosis spreads. The diversion of blood from the deeper and older channels causes a slowing of their blood stream, platelets and leucocytes become heaped up on the endothelial lining of the sinusoids (fig. 13) or the endothelium itself proliferates to obstruct the lumen. The thrombus or solid plug of endothelial cells later become hyalinized.

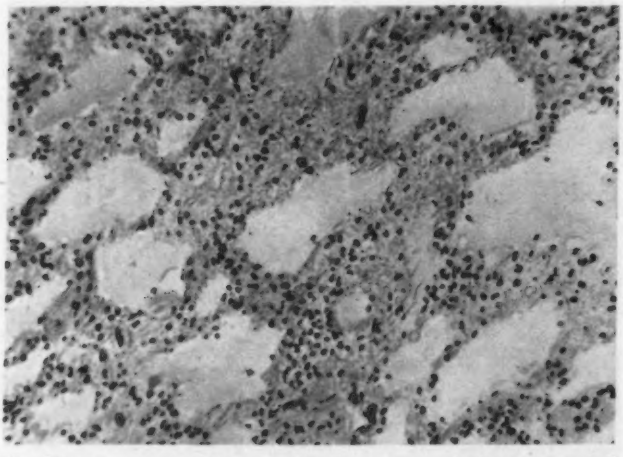


FIG. 14.—The pre-cystic state seen in the centre of the tumour of Case 5. Areas of colloid are surrounded by a fine network of astrocytes. (Hæmatoxylin eosin ×80.)

THE ANGIOARCHITECTURE OF THE RELATIVELY BENIGN GLIOMATA.

As already indicated the tumours of this group include the astrocytomata and the closely related astroblast-astrocytomata. The majority of these tumours showed either cyst formation or a pre-cystic condition on histological examination. Necrosis was not encountered. The Pickworth stain in these cases tends to give disappointing results, because not only the capillaries of the white matter but also the vessels of the tumour frequently fail to stain. The pictures only represent those areas of the tumour whose vessels contain blood corpuscles at the time of the autopsy, and in most cases a very incomplete picture has therefore been obtained.

Case 5.—History and clinical signs. F. C., aged 29, was admitted to the Neurosurgical Service of Manchester Royal Infirmary, October 29, 1937. She had been subject to frequent epilepsy for six years, and had had a coarse tremor of the right limbs for three years. Headaches had been experienced only for two months. On examination the patient was slow when answering questions, there was evidence of nominal aphasia. She had bilateral papillœdema and slight pyramidal signs of the right upper limb, and was incontinent. Angiography, November 11, showed the left anterior cerebral artery displaced a little to the right. Twelve hours later she became unconscious with increase of the right hemiplegia. Pulse and respiration rates increased, death occurred twenty-four hours later. At autopsy, a large tumour was found in the left fronto-temporal region. It measured 5 by 6 by 6 cm. and had ill-defined edges. It was firm in consistence and was slightly pinker than normal

FIG. 15.—Note the bundles of capillaries which, after looping upon themselves, terminate by joining the centrally placed venule.

white matter. At the lower and outermost part there was a small cyst which measured 2 by 2 by 1 cm.

Histological picture.—Histological examination showed that the tumour consisted of astrocytes and astroblasts. Adjoining the cyst were small masses of pink staining colloid, separated by narrow strands of tumour cells (fig. 14). This represents a pre-cystic state of the tumour. The vessels seen were capillaries; a few were surrounded by small round cells.

Angioarchitecture.—Pickworth stains demonstrated that the surrounding capillary network merged into the abnormal vascular bed of the tumour, where venules were also recognized. The capillaries were somewhat more numerous than in normal white matter, ran long distances and produced an irregular network. A tendency for the branches to run long parallel courses may be seen but was not a prominent feature of this case.

Case 6.—History and clinical findings.—E. S., aged 9, was admitted to the Neuro-surgical Service of the Manchester Royal Infirmary on February 15, 1938. For four months the patient had experienced early morning vomiting, occasional headaches, transient diplopia and a tendency to fall to the left. Examination revealed bilateral papilloedema and left-sided cerebellar signs. At operation on February 18 a cerebellar decompression was performed. The cerebellar hemisphere prolapsed, causing intense engorgement of the vessels, making it impossible to accomplish anything. The musculo-cutaneous flap was replaced, but the patient died a few hours later. At autopsy a high mid-line vermis tumour was found. It was spherical in shape and had a diameter of 4·5 cm. The cut surface was a uniform yellowish pink colour. There was no evidence of cyst formation or of necrosis.

FIG. 16.—Capillary network seen in an astrocytoma. It is important to note that this section was 350 microns in thickness. Note the parallel course taken by some of the capillaries and their branches.

Histological picture.—Histological examination showed it to be a solid astrocytoma, whose cells showed well-formed fibrillæ. There were a few microscopical hæmorrhages. The vessels appeared few, those seen had well-formed walls.

Angioarchitecture.—Pickworth stains demonstrated that in the peripheral parts of the tumour the capillaries showed the phenomena of reduplication. Groups of vessels (fig. 15), either in fours or in fives, ran side by side; these capillaries terminated by looping on themselves to join the companion venule which ran with the main wide leash of vessels. Other regions of the tumour had vessels of large uniform calibre running a comparatively straight course; these might be venules. Here again reduplicated capillaries were seen. Another part had a rich vascular bed characterized by irregularity of the network and, though capillaries predominated, venules were plentiful. Some parts of the tumour showed scarcely any

vessels, and though this may be due to the capillaries being empty of blood, it would seem from examination of ordinary histological stains that vessels were scanty.

Comments on the Angioarchitecture of the Benign Gliomata.

The pictures here presented are different from those seen in the malignant group of cases. At the periphery of the tumour the surrounding capillary network merges into the abnormal vascular bed of the tumour. The capillaries are more numerous, run long distances and

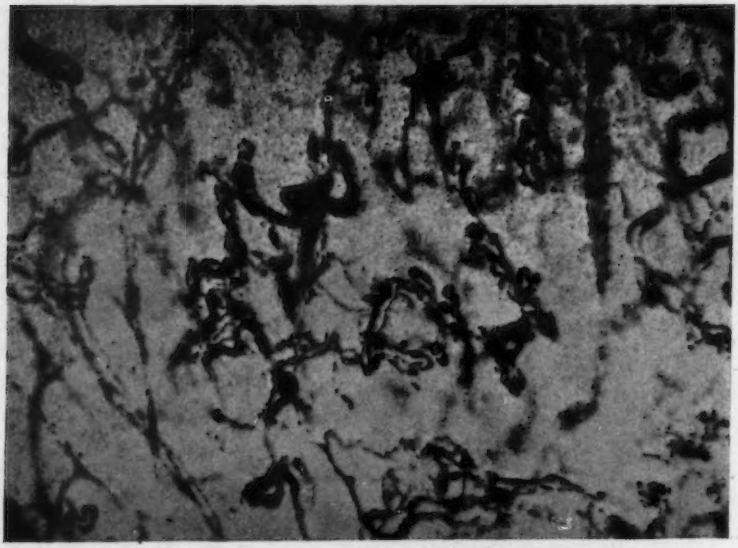


Fig. 17.—Reduplicated capillaries looped upon themselves, taken from an astrocytoma. One year previously this tumour had been diagnosed as an oligodendroglioma from material removed by operation, but only astrocytes were seen in the autopsy specimen.

form a much more irregular meshwork than that seen in normal white matter. Most of the specimens showed evidence of reduplication of the vessels. In fig. 16 two or more vessels can be seen running parallel and when one branches the companion vessel does likewise; the individual branches then continue together for some part of their course. Another type of reduplication was frequently observed where the companion vessels looped upon themselves (fig. 17). In some cases several capillaries branched, the branches ended by looping and finally joining the accom-

panying venule which ran in the centre of the leash of capillaries. These vascular arrangements appear to be typical of these tumours and are probably determined by the fact that astrocytes require a proportionate area of vessel-wall on which to implant their sucker feet. All autopsy material revealed fineness of the calibre of the capillaries. Material from two cases of frontal lobectomy was available for examination. The first was an astroblast-astrocytoma and the second a pure astrocytoma. Both these tumours were rich in capillaries and showed the phenomena of reduplication and looping, but in both the capillaries were dilated. It is realized that this material has been subjected to much manipulation during its removal. Nevertheless, it is felt that this is not the whole explanation because in the second case as the dura was reflected the vessels in the pia over the region of the tumour were observed to be dilated and more numerous than normal.

The benign gliomata are characterized by the formation of many new capillaries, as illustrated by reduplication and looping of the vessels. Since cellular proliferation is occurring slowly there is time for the blood supply to keep pace with the increase in size of the tumour, but when the tumour reaches certain dimensions it will outgrow the possibilities of the extension of the capillaries to the very centre. It is possible that the cells retain, none the less, the capacity for division, the tumour increasing its size by proliferation through its extent. Those cells at the very centre are ultimately deprived of a blood supply and when this happens islands of colloid collect within a fine meshwork of tumour cells. These areas of the tumour are diffluent and represent the pre-cystic state of an astrocytoma. In the case of malignant gliomata cyst formation is not so common and only occurs as the result of a colliquative process in the necrotic centre.

The Clinical Application of the Findings of this Study.

Moniz (1936) and Tönnis (1937) have shown that the presence of a glioblastoma multiforme may be diagnosed by the angiographic picture, a diffuse mottling indicating the hypervascularity of the tumour bed. This concentration of thorotrast may appear as a ring around the periphery of the tumour. Histological study suggests that this is brought about by thorotrast in the sinusoids which surround the large central area of necrosis. Moniz (1936) illustrated an angiogram of an astrocytoma in which the vessels of the tumour were depicted as loops, larger than the middle cerebral artery from which they sprang. This is contrary to the

writer's experience, though the dilated capillaries demonstrated in the operative material might possibly have presented a localized concentration on angiography. More commonly angiograms in cases of astrocytomata show only a displacement of the main vessels which is more in keeping with probabilities as judged by Pickworth stained material. Angiography should be employed only after considerable thought, because Northfield and Russell (1937), Ekström and Lindgren (1938) have shown that the injection of thorotrast is not without danger in tumour patients, dangers apparent in two of the cases of this series (Cases 2 and 5). Angiography would be preferable to ventriculography if by using the minimum of thorotrast one can find out not only the position, size and shape but also the type of the tumour. A useless craniotomy on a malignant tumour might then be avoided.

It would be useful to have some idea of the proportion of the malignant gliomata that might be expected to show angiographic changes. From the present study it would appear that the demonstration of mottled concentration of thorotrast around the circumference of a relatively avascular centre is diagnostic of a malignant intra-cerebral tumour. As the tumour invades the surrounding brain the central necrosis increases. The width of the living tumour depends upon the balance struck between these opposing processes. The vessel changes which one endeavours to demonstrate in an angiogram occur usually in the narrow rind of active tumour. Rough measurements carried out in this series of autopsy cases show that the thickness of this part of the tumour varies from 3 to 30 mm. This gives one some idea of the extent of the change that one is attempting to show. Of the fifteen cases in the first group, it is thought that possibly less than half would show angiographic changes and this is probably an over-estimate. Inability to show angiographic changes does not therefore exclude the presence of a malignant tumour, but when positive angiography would enable the surgeon to avoid performing craniotomy in a proportion of the unsuitable cases.

Summary.

(1) Tissues from twenty-five cases of cerebral gliomata have been studied using the Pickworth technique, together with ordinary histological stains and, in many cases, Hortega's variants. The material has been subdivided into the malignant and the relatively benign. Using Hortega's classification the malignant comprise six cases of glioblastoma heteromorph, eight glioblast-astroblastomata and one Schwanoid oligo-

dendroglioma. There were ten benign tumours, astroblast-astrocytomata and astrocytomata. The vessel changes are dependent upon the rate of proliferation of the tumour cells and thus indirectly give some indication of the degree of malignancy.

(2) In the malignant tumours there is always a large area of central necrosis surrounded by a narrow rind of living tumour. The vessels show a transition from capillaries to sinusoids which are largest and fewest at the edge of the necrosis. The necrosed centre only contains cell debris, extravasated blood and thrombosed sinusoids.

(3) Endothelial proliferation was observed in the active and superficial parts of the more malignant gliomata. In these preparations a space was found on the side of the tufts directed towards the centre of the tumour. From their peripheral aspect they were served by capillaries and venules. It is suggested that this phenomenon represents a response of the capillary wall to facilitate cellular interchange and to promote absorption of the katabolites of actively proliferating tumour cells.

(4) Adventitial proliferation is a very prominent and constant feature in all the malignant gliomata. It is most marked around the largest sinusoids bordering on the edge of the necrosis, but even the smaller more peripherally placed vessels possess a connective tissue wall of varying thickness. These observations suggest that the vessels of these tumours are formed by alteration of the pre-existing capillaries.

(5) The occurrence of central necrosis in malignant gliomata is thought to be initiated by the rapid proliferation of cells between the capillary lattice, causing partial obstruction, dilatation and rupture of the vessels, with the production of minute hæmorrhages and small foci of necrosis. Those vessels which remain patent conduct a larger volume of blood, this causes further dilatation and sinusoid formation. Widely placed sinusoids with thick adventitial walls do not encourage intercellular exchange. Further the dilated vessels cause short-circuiting of the blood from the deeper portions of the tumour so that necrosis of tumour follows in the wake of tumour cell invasion and sinusoid formation.

(6) The benign gliomata show at least histological evidence of cyst formation in nearly every case. These tumours possess only capillaries; these form a complex but irregular meshwork, characterized by reduplication and looping of the vessels. The vessels are specially produced to meet the specific needs of the tumour cells. When cell proliferation outstrips the vascular response the astrocytes degenerate and small aggregations of pink staining colloid collect between the cells, they ultimately run together and give rise to the typical astrocytomatous cyst.

(7) The clinical application of these findings lies in the interpretation of angiograms. It must be appreciated that the vessel changes are occurring in a narrow rind of living tumour varying from 3 to 30 mm. in thickness, a ring of diffuse mottling caused by concentration of thorotrast would outline a malignant tumour in the hemisphere. With the present facilities this finding will be the exception rather than the rule. However, when changes are visible the diagnosis of malignant glioma is being made on angiographic evidence with increasing assurance.

ACKNOWLEDGMENTS.

This investigation has been carried out in the Neuro-surgical Service of Manchester Royal Infirmary while working with a Research Fellowship awarded by the Medical Research Council.

I am deeply indebted to Professor Geoffrey Jefferson for the help he has given. Professor Morley kindly permitted me to carry out the technical side of the work in the Department of Surgical Reasearch of the University of Manchester. Dr. del Rio Hortega gave valuable assistance in the classification of the material for which I am very grateful.

REFERENCES.

BAILEY, P., and CUSHING, H. (1926), "Tumours of the Glioma Group." Philadelphia.
—— and EISENHARDT, L. (1932), *Jour. Comp. Neurol.*, **56**, 391.
BEEVOR, C. E. (1909), *Philos. Trans.*, **200**, 1.
CAMPBELL, A. C. P., ALEXANDER, L., and PUTNAM, T. J. (1938), *Arch. Neurol. Psychiat.* Chicago, **39**, 1151.
CARMICHAEL, E. A. (1928), *Jour. Path. Bact.*, **31**, 493.
CERLETTI, U. (1911), "Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten." Jena, **4**, 1.
CHIN, KAON (1937), *Lisboa Méd.*, **14**, 854.
DAVIS, L. (1928), *Ann. Surg.*, **87**, 8.
DEERY, E. M. (1932), *Bull. Neurol. Inst.* New York, **2**, 157.
ECHOLS, D. H. (1938), *Arch. Neurol. Psychiat.* Chicago, **39**, 494.
EKSTRÖM, V. G., and LINDGREN, A. G. H. (1938), *Zbl. Neurochir.*, **3**, 227.
ELSBERG, C. A., and HARE, C. C. (1932), *Bull. Neurol. Inst.* New York, **2**, 210.
ELVIDGE, A., PENFIELD, W., and CONE, W. (1937), "Gliomas of the Central Nervous System." "Tumours of the Nervous System." Baltimore.
FAY, T. (1925), *Jour. Amer. Med. Ass.*, **84**, 1727.
FOG, M. (1938), *Arch. Neurol. Psychiat.* London, **1**, 187.
GLOBUS, J. H., and STRAUSS, I. (1925), *Arch. Neurol. Psychiat.* Chicago, **14**, 139.
HARDMAN, J. (1938), *Lisboa Méd.*, **15**, 329.
HORTEGA, del Rio P. (1933), "Anatomia Microscopica de los Tumores del Sistema Nervioso Central y Périferico." Madrid.

HUGHES, A. F. W. (1934), *Philos. Trans.*, **224**, 75.
——(1935), *J. Anat.* London, **70**, 76.
——(1937), *Ibid.*, **72**, 1.
LEPEHNE, G. (1919), *Beitr. Path. Anat.* Jena, **65**, 163.
MCDONALD, S., and WOODHOUSE, D. L. (1938), *Path. Bact.*, **47**, 615.
MONIZ, E. (1931), "Diagnostic des Tumeurs Cérébrales et épreuve de l'Encéphalographic Artérielle." Paris.
——(1934), "L'Angiographie Cérébrale." Paris.
——(1936), *Rev. Neurol.*, **1**, 1359.
MOORE, M. T., and STERN, K. (1938), *Brain*, **61**, 70.
NORTHFIELD, D. W. C., and RUSSELL, D. S. (1937), *Lancet*, **1**, 377.
NORTHFIELD, D. W. C. (1937), *Lisboa Méd.*, **14**, 861.
——(1938), *Brain*, **61**, 132.
PFEIFER, R. A. (1928), "Die Angioarchitektonik der Grosshirnrinde." Berlin.
PICKWORTH, F. A. (1934), *J. Anat.* London, **69**, 61.
——(1938), *Brit. Med. J.*, **2**, 265.
PUTNAM, T. J. (1937), *J. Neurol. Psychopath.*, **17**, 193.
SHELLSHEAR, J. L. (1927), *Brain*, **50**, 236.
——(1930), *J. Anat.* London, **65**, 45.
SMYTH, G. E., and HENDERSON, W. R. (1938), *Arch. Neurol. Psychiat.* London, **1**, 226.
THOMA, R. (1893), "Untersuchungen über die Histogenese und Histomechanik des Gefassystems." Stuttgart.
TÖNNIS, W. (1937), *Lisboa Méd.*, **14**, 773.
TOOTH, H. H. (1912), *Brain*, **35**, 61.
WISLOCKIE, G. R., and KING, L. (1936), *Amer. J. Anat.*, **58**, 469.
WOLFF, H. G., and BLUMGART, H. L. (1929), *Arch. Neurol. Psychiat.* Chicago, **21**, 795.

DESCRIPTION OF PLATE III (facing p. 100).

FIG. 4.—A composite strip of six microscopical fields to show the changes in vessels throughout the whole thickness of the tumour, a glioblast heteromorph, from the normal brain at (A) to the necrotic centre of the tumour at (D). (× 30.)

FIG. 6.—A strip of eight microscopical fields demonstrating the vessel changes in a glioblast heteromorph. The vertical lines are artefacts incidental on the photographic technique.

FIG. 7.—The vessel changes seen in a case of glioblast-astroblastoma. (For lettering refer to text.)

FIG. 8.—The vascular changes seen in more benign glioblast-astroblastoma. (Note the capillaries distributed throughout the whole extent of the tumour.)

Notices of Recent Publications.

Textbook of Nervous Diseases. By R. Bing, translated by W. Haymaker. London: Kimpton. 1939. Pp. 838. Price 50s.

In translating the fifth German edition of Professor Bing's well-known textbook, Dr. Haymaker states that he has extensively revised and considerably augmented his original, while in a foreword Dr. Wartenberg claims that as presented by the original author "neurology has almost the exactness of mathematics," a statement that cannot be true of any branch of biology. Thus introduced and altered the book has become a congested mass of information of very unequal value, lacking that critical selection and emphasis that go to make the textbook of the first rank. The clinical descriptions swarm with superfluous eponymous signs, and the chapters on treatment with lists of multiple remedies the relative value of which is not always indicated. Over twenty substances, for example, are named as available for protein shock therapy. Nor is it clear that the re-arrangements made by the translator have always made for lucidity. Thus polyneuritis is dealt with under diseases of peripheral nerves and also under infections and intoxications, but in neither section is there an adequate clinical account of the illness. Athetosis is spoken of as a "peculiar type of motor irritation" and elsewhere as a "release" symptom. At the end of each chapter is an extensive and not well chosen bibliography, which bears no close relation to the works and authors cited in the chapter.

The photographic illustrations are of bad definition owing to the poor quality of the paper and blocks.

Yet despite the many disadvantages which the book has suffered in the processes of translation and improvement, it remains a useful work of reference for the neurologist sufficiently expert to pick his steps through the masses of information it contains, and to assess the now very variable value of its contents.

The Study of Society: Methods and Problems. Edited by F. C. Bartlett, M. Ginsberg, E. J. Lindgren and R. H. Thouless. London: Kegan Paul. 1939. Pp. 498. Price 10s. 6d.

A comprehensive review of social psychology was needed. In a subject of which the limits and methods are still uncertain, a textbook would be premature, but a critical survey of the studies, anthropological, social and psychological, which are scattered through many publications makes the present state of knowledge plain, indicates the hopeful problems and methods, and provides a valuable starting point and place of reference for further work. In the first part of this useful and well-written book general problems are stated by T. H. Pear, F. C. Bartlett, J. T. McCurdy, M. Collins and R. H. Thouless; the second part, by Blackburn, Nadel, P. E. Vernon,

Earl and Rodger is concerned with the social application of psychological studies. The third part deals with anthropological methods, as summarized by A. J. Richards, Nadel and Lindgren, and the fourth part contains articles by Clement Brown, Oeser, Farmer and A. F. Wells on some methods of sociology, concluding with a general survey by Professor Ginsberg. There is little of the repetition that is usual in symposia of this kind, and nothing of the inconsistency. The writers have discussed and harmonized their articles to good purpose. It is surprising, however, that the psychiatric contribution to the study of society has received so little attention in this otherwise comprehensive book; there is a chapter dealing with one aspect of the matter, but its author expresses the extreme view that "at the moment a knowledge of clinical psychiatry has no value for the social psychologist."

On Hereditary Ataxia and Spastic Paraplegia. By J. Bell and E. A. Carmichael. Being Volume IV, Part III of "The Treasury of Human Inheritance." London: Cambridge University Press. 1939. Pp. 281 and 32 plates. Price 17s. 6d.

This lavishly produced monograph deals with the modes of inheritance of the diseases named in its title. It will be of interest to geneticists, but its high price will deter that larger circle of neurological readers for whom it contains points of interest.

Symposium on the Synapse. By H. S. Gasser, J. Erlanger, D. V. Bronk, Lorente de Nó and A. Forbes. Reprinted from the *Journal of Neurophysiology*. Baltimore: C. C. Thomas. 1939. Pp. 472.

The various contributors to this symposium deal with the different aspects of synaptic transmission. The articles are predominantly studies in electrophysiology.

A Survey of Child Psychiatry. Contributed by Contemporary British Authorities. Edited by R. G. Gordon. London: Oxford University Press. 1939. Pp. 278. Price 10s. 6d.

This book is in four sections, dealing in turn with problems relating to physical illness, mental illness, sociological aspects and special syndromes. It was compiled with two objects: to "collect the knowledge of British experts," and "to demonstrate the extent to which Child Psychiatry had become a living subject in this country." In order to attain the former end, twenty-one contributors have been assembled—a formidable number for so small a book, and one tending to defeat its second aim. The contributors demonstrate, it is true, that child psychiatry is a living subject, but they also demonstrate the extent to which it can be diffuse and undisciplined, and prone to the faults common in medical psychology, whether it be of the psychoanalytical or of the "common-sense" variety. The contributors vary almost as much in their mode of approach to the problems as in their style and their erudition; there is much careless writing, uncritical advocacy, and repetition of elementary advice. There are, however, several illuminating chapters, and a few valuable ones. No doubt, as an introduction to the subject, this book has the merits of simplicity and variety, but it would be harsh to suppose that "contemporary British authorities" could not produce something better if they tried.

Psycho-Analysis. By EDWARD GLOVER. London: John Bale Medical Publications. 1939. Pp. 139. Price 12s. 6d.

Dr. Glover has well-known gifts for popular exposition, and this account of psycho-analysis is, like others he has written or spoken, fluent and smooth. Psycho-analysts may feel dubious at the skill he shows in gliding lightly over those sexual and other aspects of his subject which do not commend themselves to the non-analyst; but even if the presentation is a trifle emasculated, it is reasonably comprehensive and gives the reader an impression that, for Dr. Glover at any rate, psycho-analysis is an established science and an invaluable medical procedure. This follows perhaps from the statement in the introduction: "no attempt is made to argue the validity of psycho-analytical views or to give the evidence on which they are based." In short, the medical practitioner will find in this book a readable and exceptionally well-informed account of what psycho-analysts believe and claim; he can take it or leave it, but he must not expect to find in it also indications of where external criticism has fallen heavily upon the tenets and practice of psycho-analysis. For all the book says about it, such criticism might not exist.

Medizinische Psychologie. By ERNST KRETSCHMER. Fünfte Auflage. Leipzig: Thieme. 1939. Pp. 260.

Kretschmer has left his book in this edition pretty much as it was. A few paragraphs have been added; these cover the more recent views of Kleist on cerebral localization, and Kretschmer's own on constitution and on sexual development; a few passages dealing with psychotherapy have been omitted. The chief defect of the book lies in its failure to take account of criticisms and difficulties, especially in regard to those subjects, e.g. psychophysical correlation, to which Kretschmer has made original contributions.

Modern Psychotherapy. By NOEL HARRIS. London: John Bale Medical Publications. 1939. Pp. 146. Price 7s. 6d.

Any new book on psychotherapy is apt to give the reader a strong *déjà vu* feeling. This primer is not an exception. The general practitioners for whom it is intended will find it very easy to understand and free from eccentricities or abstruse language. The author evidently belongs to the "eclectic" school. It is questionable whether there is really need for more little books of this kind—ingenuously hopeful, artlessly homiletic, frankly and innocently plagiarist.

Kurzgefasstes Lehrbuch der Psychiatrie. By JOHANNES LANGE. Dritte Auflage. Leipzig: Thieme. 1939. Pp. 276.

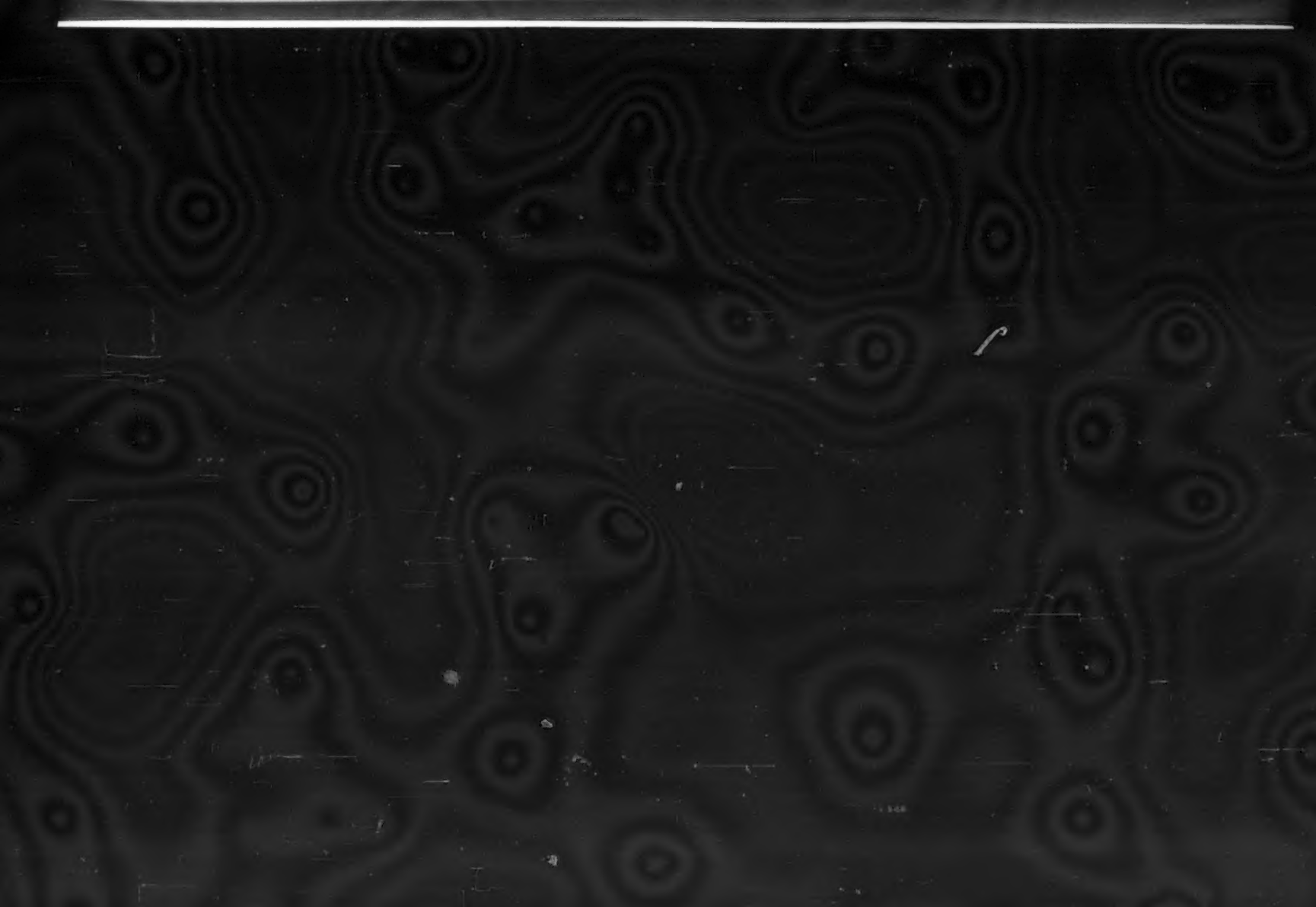
The main change in this edition of the late Professor Lange's textbook is in the chapter on epilepsy, into which the views of Manz and Stauder as to the personality and constitution of epileptics have been introduced. The ten pages devoted to treatment remain the weakest part of the book, and the neuroses are still inadequately covered. Apart from some instances of the excessive stress laid upon hereditary influences by German psychiatrists, the book is on the whole a sound compendium.

Intracranial Tumours of Infancy and Childhood. By PERCIVAL BAILEY, DOUGLAS N. BUCHANAN and PAUL C. BUCY. Chicago: The University of Chicago Press. 1939. Cambridge: The Cambridge University Press. Pp. 596 with 23 plates. Price 25s. net.

Intracranial tumours in childhood present differences from those in adult life both in their clinical aspects and in the relative frequency of different types. It is therefore valuable to have a textbook which is based, as is the present volume, on a large and representative series of cases. The first 415 pages of this volume are devoted to case histories of 100 cases of tumour arranged according to their type. This is followed by chapters on general pathology, symptomatology, operative technique and the results of treatment. This part contains less than 160 pages and of these 40 pages in the chapter on differential diagnosis are devoted to further case histories. Thus in a book of 563 pages, excluding the bibliography and indices, more than four-fifths consists of case histories. Of the chapters in the second part of the book that on pathology is disappointing as it deals chiefly with the clinical correlation of different histological types of tumour and omits any discussion of the mode of growth and spread of the tumours. The chapter on general symptomatology is the longest and best in this part of the book but suffers from discursiveness and some repetition.

The illustrations are excellent throughout and those of patients after operation, which have formed so unnecessarily large a feature of American books on cerebral tumours, are reduced to a minimum.

While the book adds little to what is generally known it should be useful as an authoritative statement of the present position of the subject with which it deals.



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